

Review Article

Epidural Anesthesia-Analgesia and Patient Outcomes: A Perspective

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The use of perioperative epidural anesthesia-analgesia may confer many benefits including superior postoperative analgesia, decreased morbidity, and improvement in patient-centered outcomes. We will review our group's work on perioperative epidural anesthesia-analgesia on patient outcomes and discuss future research in this area

1. Introduction

The use of perioperative epidural anesthesia-analgesia provides superior postoperative analgesia [1–3] versus conventional opioids, is associated with beneficial physiologic effects [4], and has been shown to improve patient-centered outcomes [5]. However, the benefits of perioperative epidural anesthesia-analgesia are not definitive in part due to some of the methodological issues present in available studies. We will review our group's work on perioperative epidural anesthesia-analgesia on patient outcomes which includes mortality, major morbidity, and patient centered outcomes but not technical failures or complications. We will also discuss future research in this area.

2. Effect on Mortality

The overall effect of epidural anesthesia-analgesia on perioperative mortality is controversial. Because of the relatively rare incidence of this endpoint, one option is to utilize a large database which would be able to capture rare outcomes such as death. We have used a 5% nationally random sample of Medicare beneficiaries (1997–2001) to examine the association between the presence or absence of postoperative epidural analgesia and perioperative (7- and 30-day) mortality [6–10]. In our initial analysis [6], we examined several surgical procedures (based on International Statistical Classification

of Diseases, Ninth Revision (ICD-9) codes) and divided patients into 2 groups, depending on the presence or absence of postoperative epidural analgesia. Mortality at 7 and 30 days after surgery was examined and multivariate regression analyses incorporating race, gender, age, comorbidities, hospital size, hospital teaching status, and hospital technology status were undertaken. Our first publication using the Medicare claims data found that the presence of epidural analgesia was associated with significantly lower odds of death at 7 days (odds ratio (OR) = 0.52; 95% confidence interval (CI): 0.38–0.73; $P = 0.0001$) and 30 days (OR = 0.74; 95% CI: 0.63–0.89; $P = 0.0005$) postoperatively, thus suggesting that postoperative epidural analgesia may contribute to lower odds of death after surgery [6].

Subsequent analyses of the Medicare claims data also revealed that the presence of postoperative epidural analgesia may be associated with lower perioperative mortality in patients undergoing higher-risk surgical procedures (e.g., lung lobectomy, colectomy) [7, 8]. In a cohort of 3501 Medicare patients who underwent nonemergency segmental excision of the lung, multivariate regression analysis showed that the presence of epidural analgesia was associated with significantly lower odds of death at 7 days (OR = 0.39; 95% CI: 0.19–0.80; $P = 0.001$) and 30 days (OR = 0.53; 95% CI: 0.35–0.78; $P = 0.002$) after surgery, again suggesting that postoperative epidural analgesia may contribute to lower odds of death [7]. Similarly, we examined a cohort of 12,817 Medicare

patients who underwent elective partial excision of the large intestine [8]. Multivariate regression analysis revealed that the presence of epidural analgesia was associated with significantly lower odds of death at 7 days (OR = 0.35; 95% CI: 0.21–0.59; $P < 0.0001$) and 30 days (OR = 0.54; 95% CI: 0.42–0.70; $P < 0.0001$) after surgery [8]. However, our analyses of Medicare patients undergoing lower-risk procedures (e.g., total hip and total knee replacement) showed that the use of postoperative epidural analgesia was not associated with a lower incidence of mortality and major morbidity [9, 10].

Other groups have also performed similar analyses on other databases. A Canadian group examined 259,037 patients (≥ 40 years of age) who underwent selected elective intermediate-to-high risk noncardiac surgical procedures [11]. A matched-pairs cohort was performed and found that epidural anesthesia-analgesia was associated with a reduction in 30-day mortality (relative risk (RR) = 0.89, 95% CI: 0.81–0.98, $P = 0.02$) although the overall absolute magnitude of the finding was small, corresponding to a number needed to treat of 477 [11]. The largest meta-analysis [12] and randomized controlled trials (RCTs) [13, 14] on this topic provide mixed results on whether epidural anesthesia-analgesia decreases perioperative mortality.

3. Effect on Conventional Morbidities

Perioperative epidural anesthesia-analgesia utilizing a local anesthetic-based regimen clearly provides some physiologic benefits which may potentially translate into decreased perioperative pulmonary, cardiac, and gastrointestinal morbidity [4, 15]. A recently published meta-analysis indicated that perioperative epidural anesthesia-analgesia is associated with significantly lower risk of heart block, atrial fibrillation, supraventricular tachycardia, respiratory depression, pneumonia, atelectasis, sedation, ileus, dizziness, and postoperative nausea and vomiting although there was a higher risk of pruritus (with epidural opioids), urinary retention, and hypotension [15]. Uncontrolled pain, surgical disruption of the thoracoabdominal musculature, and spinal reflex inhibition of the phrenic nerve [4] may contribute to atelectasis and pulmonary morbidity. Although our prior Medicare analyses did not demonstrate a benefit for epidural analgesia in decreasing pneumonia or other pulmonary complications [7], several meta-analyses of RCTs all indicate that perioperative epidural analgesia is associated with a decrease in postoperative pulmonary complications including pneumonia [16, 17]. Our meta-analysis in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass noted that patients who were randomized to receive thoracic epidural analgesia had significantly reduced odds of pulmonary complications (OR = 0.41; 95% CI: 0.27–0.60, $P < 0.0001$) and time to tracheal extubation by 4.5 h ($P = 0.0005$) [18].

Use of epidural anesthesia-analgesia may also result in an improvement in cardiac outcomes. A local anesthetic-based regimen may improve subendocardial coronary blood flow and decrease pain. Pain may increase myocardial oxygen demand (and thus potentially myocardial ischemia) [4]. Several meta-analyses of RCTs suggest that use of epidural anesthesia-analgesia may be associated with a decrease in

perioperative cardiac outcomes particularly dysrhythmias and possibly myocardial infarction [19, 20]. Our own meta-analysis in patients undergoing coronary artery bypass surgery found that patients who were randomized to receive thoracic epidural analgesia had significantly reduced odds of dysrhythmias (OR = 0.52; 95% CI: 0.29–0.93, $P = 0.03$) but not myocardial infarction (OR = 0.74; 95% CI: 0.34–1.59, $P = 0.44$) [18].

Finally, perioperative use of epidural anesthesia-analgesia with a local anesthetic-based solution may facilitate return of gastrointestinal (GI) function. By minimizing use of opioids (which can inhibit GI motility) and blocking sympathetic outflow (which allows for unopposed parasympathetic outflow), epidural analgesia may be the optimal postoperative analgesic regimen for patients with abdominal surgery. Several systematic reviews indicate that epidural anesthesia-analgesia for abdominal surgery is associated with significantly reduced pain scores and duration of ileus (weighted mean difference (WMD) = -1.55 d; 95% CI: -2.27 to -0.84 d) [21, 22]. This benefit was apparent when comparing epidural local anesthetic regimens versus epidural or systemic opioid analgesia [22]. Our own work in patients undergoing colon surgery indicated that patients who received patient-controlled epidural analgesia (PCEA) (versus intravenous morphine patient controlled analgesia (IV PCA)) had better analgesia and fulfilled discharge milestones approximately 36 hours faster ($P < 0.002$) [23].

4. Effect on Patient-Centered Outcomes

Although many of the available published studies have focused on conventional or traditional outcomes such as mortality and morbidity, there has been increasing interest in patient-centered outcomes such as satisfaction, quality of recovery, and analgesia. There is great potential for perioperative epidural anesthesia-analgesia (versus systemic opioids) in improving patient-centered outcomes [5] as the profile for a local anesthetic-based epidural analgesic regimen could potentially confer many favorable advantages (e.g., lower pain scores, less nausea/vomiting) to facilitate patient recovery.

The available data clearly indicates that epidural analgesia with a local anesthetic-based regimen provides superior analgesia (i.e., significantly lower pain scores) compared to systemic opioids [1, 2]. We have shown that epidural analgesia provided significantly better postoperative analgesia compared with parenteral opioids on each postoperative day for up to three days postoperatively [1]. In comparing the “gold standards” for analgesia (i.e., PCEA versus IV PCA with opioids), our group found that PCEA provided significantly superior postoperative analgesia compared with IV PCA [2]. The superior analgesia provided by epidural analgesia may result in improvements in other aspects of patient-centered outcomes particularly quality of life and quality of recovery.

Although it is not clear whether the use of perioperative epidural anesthesia-analgesia would be associated with an improvement in postoperative patient satisfaction [24] or cognitive function [25] due to the complex multidimensional nature of these outcomes, it is clear that an increase in postoperative pain is associated with a decrease in patients’

health-related quality of life (HRQL) and quality of recovery (QoR) in the immediate postoperative period [26, 27]. In a prospective, nonrandomized, observational trial in patients undergoing elective total hip or knee replacement surgery, we found that severity of pain correlated with a decrease in both the physical and mental component of the short form 12 (SF-12), a common instrument used to assess quality of life [26]. An increase in postoperative pain has been shown to correlate to a decrease in a patient's quality of life in the immediate postoperative period [25]. In a subsequent prospective, observational study in patients undergoing elective radical retropubic prostatectomy, we found that the severity of pain both at rest and with activity correlated with a decrease in quality of recovery (QoR), a validated instrument used to assess a patient's quality of recovery in the immediate postoperative period [27].

There are many benefits conferred by the perioperative epidural analgesia, which is best utilized as part of a multimodal analgesia regimen. Typically, multimodal analgesia incorporates several other analgesic modalities including nonsteroidal anti-inflammatory agents, gabapentanoids [28], and other agents [29, 30]. A multimodal analgesic regimen may also include agents to suppress some of the analgesic-(opioid-) related side effects such as nausea/vomiting [31] or pruritus [32]. Finally, epidural analgesia is best utilized as part of an enhanced recovery after surgery program as the superior analgesia and minimization of opioids will facilitate patient recovery [33].

5. Methodological Issues

Despite several decades of research, we are still uncertain whether the use of perioperative epidural anesthesia-analgesia may definitively improve traditional patient outcomes such as mortality or major morbidity. A large part of this uncertainty reflects the limitation of different study designs when studying the "regional anesthesia versus general anesthesia" question. We have utilized several study designs (i.e., randomized controlled trials, meta-analysis, and database analysis) in our attempt to answer this question.

Randomized controlled trials are considered the "gold standard" for determining causality (i.e., cause and effect relationship) between an intervention (e.g., epidural anesthesia-analgesia) and outcome (e.g., death or major morbidity). We have used the randomized controlled trial format [23] in examining the effect of perioperative epidural anesthesia-analgesia and gastrointestinal outcomes. However, there are several limitations of the randomized controlled trial study design when using it to address the "regional anesthesia versus general anesthesia" question. One of the main limitations is the need for large sample sizes particularly when the primary outcome is rare such as death. For instance, approximately 24,000 subjects would need to be recruited for a study using relatively high-risk patients [34] and over 1,000,000 subjects would be needed for a lower-risk population [27, 35]. Another limitation is that a randomized controlled trial typically protocolizes patient care which by itself might influence outcomes (e.g., tight control of heart rate and blood pressure).

Another way to study the "regional anesthesia versus general anesthesia" question is to use meta-analysis which in essence combines data from several randomized controlled trials to create a single pooled estimate. Our group has undertaken several meta-analyses [1, 2, 17]. The advantage is that there is increased statistical power to detect treatment differences especially as many of the randomized controlled trials in this area are underpowered and have inadequate sample sizes. Another advantage of meta-analysis is the relatively lower cost (compared to a similarly sized randomized controlled trial) and possibility of doing subgroup analysis. However, there are several limitations to meta-analyses including the fact that the final result in part depends on the quality of published data available. In addition, there may be significant heterogeneity and publication bias present. Finally, one of the main problems with meta-analyses is that this study design may oversimplify a complex issue and in some ways may be best for generating further hypotheses for future research.

A final method to examine the effects of perioperative epidural anesthesia-analgesia on patient outcomes is database analysis, which technically is considered a type of observational study. We have used the Medicare claims database to examine the correlation between epidural analgesia and patient mortality [6–9]. There are other national, administrative, or societal databases that may be used for this purpose. The advantage of using databases to examine a rare outcome such as death is that these databases contain information about very large numbers of subjects. In addition, data acquisition takes less time and costs less compared to a similarly sized randomized controlled trial. Finally, this type of study exhibits strong external validity as it is derived from actual clinical practice data. However, there are several disadvantages of database analysis including the fact that these databases are typically not designed for research purposes and as such may have limited information on diagnosis or complications. Finally, any positive findings from database analysis are only correlations; that is, this type of analysis can only propose associations, not causation.

6. Areas for Future Research

There are several areas of potential investigation for epidural analgesia and patient outcomes. Two clinical areas that are potentially interesting for epidural analgesia are obstructive sleep apnea (OSA) and cognitive function/delirium. For OSA, the at-risk factor is obesity which is an increasing problem in industrialized nations. The majority of OSA patients that present for surgery are undiagnosed although there are many methods that have been proposed to stratify risk in these patients [36]. Epidural analgesia utilizing a local anesthetic only regimen (along with nonopioid adjuvants) would seem to be the ideal postoperative regimen; however, no appropriately sized and designed randomized controlled trials have been conducted in this important area.

One of the most feared postoperative complications in the elderly surgical patient is postoperative cognitive function and delirium. Although the pathophysiology and etiology of these complications are uncertain, epidural analgesia may be of benefit as increased pain levels and opioids have been

associated with a higher rate of these complications [37, 38]. Again, very few studies have been performed investigating the use of epidural analgesia in this area particularly with PCEA utilizing a local anesthetic-based solution. Even though our initial work [25] suggested that use of epidural or spinal anesthesia did not have a benefit in reducing postoperative cognitive function or delirium, there are significant methodological issues (presence of a confounder such as the use of a benzodiazepine) with available studies and few have properly studied the role of postoperative epidural analgesia on postoperative cognitive function and delirium.

A final area for additional research would be the use of epidural anesthesia-analgesia as part of a multidisciplinary approach to enhanced recovery after surgery (ERAS), surgical site infection, and cancer recurrence. Use of epidural anesthesia-analgesia in these multidisciplinary pathways has been shown to decrease hospital length of stay and incidence of complications for patients undergoing open colorectal surgery [33, 39]. Epidural anesthesia-analgesia is an important component of an ERAS pathway as the superior opioid-sparing analgesia provided by this technique allows the patient to mobilize and facilitate earlier return of gastrointestinal function. In addition, the use of epidural anesthesia-analgesia with local anesthetics attenuates the neuroendocrine stress response and preserves perioperative immune function for the surgical patient.

The physiologic benefits of epidural anesthesia-analgesia underlying the principles of ERAS, cancer recurrence, and surgical site infection initiatives include preservation of perioperative immune function, provision of superior postoperative analgesia, and minimization of perioperative opioid use. Use of perioperative epidural anesthesia-analgesia (compared to general anesthesia and systemic opioids) has been shown to be associated with a decrease in cancer recurrence and surgical site infection [40, 41]. We are in the process of undertaking and studying a multidisciplinary approach to take advantage of the physiologic benefits of epidural anesthesia-analgesia and maximize nonopioid adjuvant agents [28, 30] in an attempt to decrease hospital length of stay and surgical complications including surgical site infection and cancer recurrence.

7. Summary

Although many investigators and clinicians will focus on the effect of epidural anesthesia-analgesia on perioperative outcomes, we must recognize that epidural anesthesia-analgesia is only one of many possible factors that may affect perioperative outcome, and a multimodal or multidisciplinary regimen may provide the best approach for our patients. Although there are many benefits for epidural anesthesia-analgesia in improving perioperative outcomes, the benefits and risks of perioperative epidural analgesia should be individualized for each patient [42, 43].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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