The Association of Intraoperative Factors with the Development of Postoperative Delirium

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PURPOSE: To examine the association of intraoperative factors, including route of anesthesia, hemodynamic complications, and blood loss, with the development of postoperative delirium.

PATIENTS AND METHODS: We studied 1,341 patients 50 years of age and older admitted for major elective noncardiac surgery at an academic medical center. Data on route of anesthesia, intraoperative hypotension, bradycardia and tachycardia, blood loss, number of blood transfusions, and lowest postoperative hematocrit were obtained from the medical record. Delirium was diagnosed by using daily interviews with the Confusion Assessment Method, as well as from the medical record and the hospital’s nursing intensity index.

RESULTS: Postoperative delirium occurred in 117 (9%) patients. Route of anesthesia and intraoperative hemodynamic complications were not associated with delirium. Delirium was associated with greater intraoperative blood loss, more postoperative blood transfusions, and postoperative hematocrit <30%. After adjusting for preoperative risk factors, postoperative hematocrit <30% was associated with an increased risk of delirium (odds ratio = 1.7, 95% confidence interval 1.1–2.7).


Delirium is one of the most common complications after surgery in older persons (1). In addition, causing distress to patients, family members, and providers, it has been associated with adverse postoperative outcomes, including major complications, poor functional and cognitive recovery, increased length of stay, and greater cost (2–5). Some have suggested that delirium plays a central role in the cascade of adverse events that affect many hospitalized elderly, culminating in functional decline and loss of independence (6). Several studies have reported risk factors for postoperative delirium (7–9). We have previously derived and validated a preoperative clinical prediction rule that includes advanced age, cognitive and functional impairment, history of alcohol abuse, markedly abnormal serum chemistry values, and aortic aneurysm or thoracic surgery (2).

In this study, we examined the effect of intraoperative factors, including route of anesthesia, presence of hemodynamic complications, and blood loss on the subsequent incidence of delirium. Although mortality during surgical anesthesia has become exceedingly low, intraoperative events still affect postoperative morbidity and mortality (10). With close intraoperative monitoring, early intervention during surgery might prevent delirium, thereby avoiding subsequent adverse events.

METHODS

Subjects
The sample consisted of 1,341 patients who were enrolled in the previously published prospective study of subjects older than 50 years of age admitted to Brigham and Women’s Hospital for major elective noncardiac surgery (2). Eighty-six of 88 surgeons at our institution gave us permission to approach their patients, and 1,341 (84%) of 1,596 approached patients agreed to participate. The study was approved by our Institutional Review Board, and informed consent was obtained.

Preoperative Interviews
All patients underwent preoperative evaluations by study personnel that included a detailed review of past medical history, physical examination, cognitive status assessment using the Telephone Interview for Cognitive Status (11), physical functional status assessment using the Specific Activity Scale (12), and laboratory tests (2).

Data Collection on Intraoperative Factors
Intraoperative data were recorded from the medical record before the development of delirium. The anesthe-
sia record was reviewed to determine the route and agent of anesthesia employed. Routes included general, spinal, epidural, and combinations. Within each route, there was little variation in the anesthetic agents used (isoflurane for general anesthesia, bupivicaine for spinal, and lidocaine or bupivicaine with fentanyl for epidural anesthesia), so each route was considered as a single group.

Intraoperative data from the anesthesia record were also reviewed. Hypotension was defined as a blood pressure decline to <66% of preoperative baseline or <90 mm Hg requiring pressors or fluid resuscitation. The duration of hypotension was also recorded. We defined bradycardia as a heart rate of <60 beats per minute requiring atropine, and tachycardia as a heart rate of >120 beats per minute lasting longer than 5 minutes. We also recorded the estimated intraoperative blood loss.

Detection of Delirium
All patients underwent daily structured interviews by study personnel on postoperative days 2–5, or until the day before discharge for patients leaving before the sixth postoperative day. The brief interview tested orientation and attention and was well tolerated during repeated administration (2). Interviews were not performed after postoperative day 5 because of the low incidence of delirium after this time. Information on changes in mental status was also collected daily from the medical record and from the hospital’s nursing intensity index. This index measures the nursing resources required to manage an individual patient and includes daily information on the patient’s mental status recorded by the primary nurse (13). Medical record and nursing intensity index review were continued for the duration of the hospitalization.

Diagnosis of Delirium
As previously reported (2), patients were classified as having delirium if they met one of the criteria described below on at least one day after the first postoperative day. Two criteria were used because of delirium’s fluctuating nature. Postoperative day one was excluded because of difficulty differentiating delirium from residual anesthesia effect. The Confusion Assessment Method (14) required a diagnosis of delirium using the specific diagnostic algorithm during daily postoperative interviews. A primer developed by the authors was used to train study personnel in its use.

The Chart/Nursing Intensity Index criteria required documentation of altered mental status in both the medical record and in the nursing intensity index on the same day, thereby increasing the specificity for delirium. Our previous work demonstrated that patients diagnosed with delirium using these two criteria had similar risk factors and outcomes (2), supporting the validity of combining them into a single endpoint.

Association of Postoperative Hematocrit with Delirium
The association of postoperative hematocrit with delirium was examined using the lowest postoperative hematocrit that was recorded in the hospital’s computerized laboratory database at least 1 day before the onset of delirium in the patients who developed delirium, or throughout the entire postoperative period in the patients who did not. These values had been measured at the discretion of the treating physician. Postoperative hematocrit data were available on 1,266 (94%) of 1,341 patients. We also used the hospital information system to obtain the number of units of blood transfused from the start of surgery to hospital discharge. Unfortunately, the precise timing of these transfusions was not available, so we were unable to ascertain whether they were performed before or after the onset of delirium.

Data Analysis
Univariate associations of the intraoperative factors of interest with delirium were analyzed using chi-square tests and Student’s t tests. Continuous data are presented as mean ± SD, unless otherwise noted. Lowest postoperative hematocrit was analyzed as a continuous variable, as an ordered categorical variable, and dichotomized at 30%, the point at which tissue oxygen delivery declines in the postoperative state (15). The independent associations of the intraoperative risk factors with delirium were determined using logistic regression, adjusting for preoperative risk factors for delirium using our clinical prediction rule (2). Odds ratios (OR) with 95% confidence intervals (CI) are reported. Because intraoperative blood loss and number of transfusions were highly collinear with lowest postoperative hematocrit, it would not be appropriate to combine these in a multivariable model. Since hematocrit is most amenable to a perioperative intervention by an internist, it was selected for inclusion in the model.

RESULTS
Patients had a mean age of 67 ± 9 years. Slightly more than half (55%) were women. They underwent a variety of procedures: orthopedic in 578 (43%); vascular in 191 (14%); abdominal in 171 (13%); noncardiac thoracic in 123 (9%); aortic aneurysm in 55 (4%); and miscellaneous (urologic, gynecologic, or breast) in 223 (17%). Most patients received general anesthesia, often in combination with epidural anesthesia (Table 1). The length of hospital stay was 8 ± 5 days (median ± interquartile range).

About one-fourth of patients had intraoperative hypertension (n = 352, 26%); bradycardia occurred intraoperatively in 49 (4%) patients, and tachycardia in 47 (4%). Mean intraoperative blood loss was 566 ± 890 cc, number of blood transfusions was 1.3 ± 2.4 units, and the
The lowest postoperative hematocrit was 30% ± 5%. Seven hundred twenty-eight patients (58%) had a lowest postoperative hematocrit, 30%. Incidence of Delirium

Delirium developed on or after postoperative day 2 in 117 (9%) patients. Of these, 19 met Confusion Assessment Method criteria, 44 met Chart/Nursing Intensity Index criteria, and 54 met both criteria. Most cases (83%) were diagnosed on postoperative days 2 (n = 72) and 3 (n = 25).

Associations of Delirium with Route of Anesthesia and Intraoperative Complications

The incidence of delirium after each of the routes of anesthesia was similar (Table 1). There was also no association between route of intraoperative anesthesia and postoperative delirium in any high-risk subgroups for delirium) or after adjusting for overall preoperative risk using our clinical prediction rule.

The incidence of delirium among subjects who had intraoperative hemodynamic complications did not differ from that in patients who did not have these complications (Table 2). Duration of hypotension was also not associated with the incidence of delirium. There were no associations found between delirium and route of anesthesia or hemodynamic complications in any high-risk subgroups, or after adjusting for overall postoperative risk.

**Table 1. Association of Postoperative Delirium with Route of Intraoperative Anesthesia**

<table>
<thead>
<tr>
<th>Route of Anesthesia</th>
<th>N Patients</th>
<th>N with delirium</th>
<th>Incidence of Delirium*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>582</td>
<td>42</td>
<td>7%</td>
</tr>
<tr>
<td>General/epidural</td>
<td>336</td>
<td>34</td>
<td>10%</td>
</tr>
<tr>
<td>Epidural</td>
<td>252</td>
<td>26</td>
<td>10%</td>
</tr>
<tr>
<td>Spinal</td>
<td>106</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>59</td>
<td>7</td>
<td>12%</td>
</tr>
</tbody>
</table>

* P = 0.33 by chi-square test.

**Table 2. Association of Postoperative Delirium with Intraoperative Hemodynamic Complications**

<table>
<thead>
<tr>
<th>Intraoperative Complication</th>
<th>N Delirious</th>
<th>N with Complication</th>
<th>N without Complication</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension*</td>
<td>27/352 (8%)</td>
<td>90/989 (9%)</td>
<td>0.8</td>
<td>0.5–1.3</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Bradycardia†</td>
<td>4/49 (8%)</td>
<td>113/1292 (9%)</td>
<td>0.9</td>
<td>0.3–2.6</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Tachycardia‡</td>
<td>5/47 (11%)</td>
<td>112/1294 (9%)</td>
<td>1.3</td>
<td>0.5–3.3</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

* Systolic blood pressure <2/3 of preoperative baseline or <90 mm Hg requiring pressors or fluid resuscitation.
† Heart rate <60 beats per minute requiring atropine.
‡ Heart rate >120 beats per minute lasting 5 or more minutes.

**DISCUSSION**

We found that the route of anesthesia and intraoperative hemodynamic complications, including hypotension, tachycardia, and bradycardia, were not associated with subsequent development of delirium. Intraoperative blood loss, number of postoperative blood transfusions and lowest postoperative hematocrit <30% were associated with delirium.

Several previous studies have found that the route of intraoperative anesthesia is not associated with postoperative cognitive dysfunction (16–22). Our study confirms and extends these findings by using daily postoperative interviews and a validated diagnosis of delirium as the primary outcome.

Intraoperative hemodynamic complications, particularly hypotension, have been thought to contribute to postoperative complications (23). However, a preliminary study performed in this same cohort did not find an association between intraoperative hypotension and postoperative cardiac complications. In the current analysis, we found no association between hemodynamic complications and delirium. It is likely that current state-of-the-art intraoperative monitoring has allowed prompt associations...
recognition and treatment of these hemodynamic abnormalities, thus limiting their sequelae.

The associations of blood loss and low hematocrit with major complications and functional recovery have been examined following major cardiac and vascular surgery (24–26). The results have been mixed, although one study has shown an association between low hematocrit and cardiac morbidity in high-risk patients (26). Low postoperative oxygen saturation has been associated with postoperative delirium (27), although a recent study by the same authors did not find an association with cognitive dysfunction 1 week and 3 months after surgery, an outcome somewhat different from delirium (28). Although routine oxygen saturation measurements were not available in our study, low postoperative hematocrit might cause delirium by the same mechanism: inadequate delivery of oxygen to the brain.

Our findings have implications for surgeons, anesthesiologists, and other physicians involved in the care of older patients undergoing major elective surgery. Route of intraoperative anesthesia is unlikely to affect postoperative delirium; medications given during the postoperative period, especially analgesics, are more important (28). Although routine oxygen saturation measurements were not available in our study, low postoperative hematocrit might cause delirium by the same mechanism: inadequate delivery of oxygen to the brain.

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In our study, patients who developed delirium had greater intraoperative blood loss and received more postoperative transfusions. Despite the transfusions, patients whose hematocrit fell below 30% were more likely to develop delirium. Our interpretation is that a low hematocrit in the perioperative setting is likely to cause a central nervous system insult that predisposes to delirium. Evaluation of whether a transfusion strategy to prevent the postoperative hematocrit from falling below 30% can re-

Table 4. Multivariable Predictors of Delirium

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest postoperative hematocrit &lt;30%</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td>.03</td>
</tr>
<tr>
<td>Age ≥70 years old</td>
<td>2.8</td>
<td>1.6–4.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Cognitively impaired*</td>
<td>4.1</td>
<td>2.6–6.5</td>
<td>.0001</td>
</tr>
<tr>
<td>Limited physical function*</td>
<td>3.1</td>
<td>1.7–5.7</td>
<td>.0001</td>
</tr>
<tr>
<td>History of alcohol abuse</td>
<td>2.8</td>
<td>1.2–6.3</td>
<td>.02</td>
</tr>
<tr>
<td>Markedly abnormal serum chemistry values†</td>
<td>2.3</td>
<td>1.0–5.1</td>
<td>.04</td>
</tr>
<tr>
<td>Intrathoracic surgery</td>
<td>3.0</td>
<td>1.6–5.6</td>
<td>.001</td>
</tr>
<tr>
<td>Abdominal aneurysm surgery</td>
<td>9.1</td>
<td>1.1–2.7</td>
<td>.0001</td>
</tr>
</tbody>
</table>

* Defined as a score <30 on Telephone Interview for Cognitive Status (11).
† Defined as Class IV on Specific Activity Scale (12).
‡ Defined as a sodium <130 or >150 meq/L, potassium <3.0 or >6.0 meq/L, or glucose <60 or >300 meq/L.

Table 3. Association of Postoperative Delirium with Intraoperative Blood Loss and Postoperative Hematocrit*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Delirium (n = 117)</th>
<th>No Delirium (n = 1,224)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean intraoperative blood loss (cc) (odds ratio per 1,000 cc)</td>
<td>1,150 ± 1,860</td>
<td>510 ± 710</td>
<td>1.6</td>
<td>1.4–1.9</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Blood transfusions (units) (odds ratio per unit)</td>
<td>3.3 ± 5.6</td>
<td>1.2 ± 1.8</td>
<td>1.3</td>
<td>1.2–1.4</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Lowest postoperative hematocrit Hematocrit (%) (odds ratio per 1%)</td>
<td>29 ± 4</td>
<td>30 ± 5</td>
<td>0.93</td>
<td>0.9–0.98</td>
<td>.001†</td>
</tr>
<tr>
<td>&gt;32%</td>
<td>22 (19%)</td>
<td>351 (31%)</td>
<td>—</td>
<td>1.1–1.3</td>
<td></td>
</tr>
<tr>
<td>30–32%</td>
<td>12 (10%)</td>
<td>161 (14%)</td>
<td>1.2</td>
<td>1.3–3.3</td>
<td></td>
</tr>
<tr>
<td>28–30%</td>
<td>25 (21%)</td>
<td>194 (17%)</td>
<td>2.0</td>
<td>1.3–3.8</td>
<td></td>
</tr>
<tr>
<td>25–28%</td>
<td>42 (36%)</td>
<td>305 (27%)</td>
<td>2.2</td>
<td>1.2–2.8</td>
<td>.004†</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>16 (14%)</td>
<td>138 (12%)</td>
<td>1.8</td>
<td>1.3–3.0</td>
<td></td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>Yes</td>
<td>83 (71%)</td>
<td>637 (55%)</td>
<td>2.0</td>
<td>1.3–3.0</td>
</tr>
<tr>
<td>No</td>
<td>34 (29%)</td>
<td>512 (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Lowest postoperative hematocrit before the onset of delirium in patients who developed delirium and throughout the entire postoperative period in those who did not. Postoperative hematocrit values were obtained in 1,266 of 1,341 patients enrolled in this study, including all 117 patients who developed delirium.
† t test.
‡ Odds ratios calculated with hematocrit >32% group as the reference.
§ Chi-square test for trend.
|| Chi-square test.
duce delirium should be undertaken in high-risk patients.

Our study has several limitations. Most notably, these associations may not be cause–effect. Lower postoperative hematocrit may be a marker for other unrecognized factors that increase the risk of delirium. Second, although we previously found an association between postoperative psychoactive medications and delirium (29), medication information was not available in the current analysis. Third, delirium was not examined on postoperative day 1; therefore, we could have missed mild, transient episodes of “emergence delirium.” However, using our validated methods, we believe that we diagnosed all clinically important cases of delirium. Fourth, postoperative hematocrit values were drawn at the discretion of the treating physician rather than as part of the study. Although <6% of patients had no postoperative hematocrit values (all patients who developed delirium had hematocrit values), sicker patients may have had more frequent testing and a greater “opportunity” to have a low hematocrit. Finally, because this study was performed in elective surgery patients at a tertiary care institution, the results may not generalize to other populations, particularly high-risk elderly undergoing emergency surgery.

In this study, delirium was associated with a postoperative hematocrit <30%. Because delirium is a syndrome of multifactorial etiology, factors in addition to hematocrit must be addressed. However, our data suggest that a transfusion strategy to keep hematocrit >30% should be one component of a multifactorial intervention to prevent delirium. The effectiveness of such an intervention should be tested by an appropriately designed trial.

REFERENCES