Perioperative Stroke Risk in Nonvascular Surgery

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Key Words
Perioperative stroke · General surgery · Risk factors · Antithrombotic therapy

Abstract
Background: Perioperative stroke is an ischemic or hemorrhagic cerebrovascular accident that can arise intraoperatively or from 3 to 30 days after surgery. This relatively rare complication deserves attention because of its high mortality and serious disability, the latter of which can lead to prolonged hospital stay as well as discharge to long-term care facilities. The aim of this article was to review the literature on perioperative stroke in general surgery, excluding carotid and cardiac surgeries because these have already been thoroughly investigated in previous papers. Methods: A search strategy was designed to identify all relevant studies on perioperative stroke in the English language. This search was restricted to papers published up to December 5, 2011. Studies were initially identified from the Medline/PubMed database, EMBASE and the Cochrane Database using the search terms ‘surgery’, ‘perioperative stroke’, ‘risk factors’, ‘anticoagulation treatment’ and ‘antiplatelet treatment’. Results: The incidence of perioperative stroke among patients who undergo nonvascular surgery is reported to be about 0.08–0.7%. This depends on the type and complexity of the surgical procedure along with patient risk factors. The reported perioperative mortality is 18–26%. One of the main issues is the management of patients taking anticoagulant or antiplatelet drugs, as the risk of bleeding has to be counterbalanced with the risk of arterial thrombosis due to discontinuation. Additionally, the presence of symptomatic carotid stenosis should be taken into account in the risk evaluation. Conclusions: To date, current guidelines are incomplete regarding the management of patients with vascular disease undergoing nonvascular surgery. It is recommended to stop oral anticoagulation approximately 5 days before major surgery to adequately allow the INR to normalize, and at the same time subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin should be started. Regarding new anticoagulants, dabigatran does not need to be withheld for minor procedures. Currently, there are no clear recommendations on the use of rivaroxaban and apixaban. Data concerning the management of patients undergoing antiplatelet therapy are lacking. To date, neurologists discourage the perioperative withdrawal of aspirin (acetylsalicylic acid, ASA) especially in patients in secondary prevention. The ‘Antiplatelet Agents in the Perioperative Management of Patients Trial’ is ongoing to assess the safety and determine the optimal use of ASA in the perioperative management of patients undergoing general and abdominal surgery. In the meantime an individualized, accurate, multidisciplinary (surgical, neurological, cardiological and anesthesiological) risk/benefit assessment remains the best basis for treatment decision.

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Introduction

Perioperative stroke is an ischemic or hemorrhagic cerebrovascular accident that can arise intraoperatively or from 3 to 30 days after surgery [1]. It is a relatively rare complication of surgical interventions which deserves attention because of its high mortality and serious disability that can lead to both prolonged hospital stay as well as discharge to long-term care facilities [2, 3]. Furthermore, the real incidence is most likely underestimated as the neurological deficits may be mild, transient or misdiagnosed because sedatives and narcotics often hinder neurological assessment [1, 4].

The aim of this article was to review the literature on perioperative stroke in general surgery, excluding carotid and cardiac surgeries because these have already been thoroughly investigated in previous papers [2, 5–14].

Materials and Methods

A search strategy was designed to identify all relevant studies on perioperative stroke in the English language. This search was restricted to papers published up to December 5, 2011. Studies were initially identified from the Medline/PubMed database, EMBASE and the Cochrane Database using the search terms 'surgery', 'perioperative stroke', 'risk factors', 'antiplatelet treatment' and 'antiplatelet treatment'. One of the researchers (F.M.) read all of the abstracts in order to choose pertinent papers for this review. If any doubt was raised on the pertinence of an article, a second opinion was requested from another author (V.C.).

Results

Of the 3,352 papers found during the literature search only 57 (33 studies and 24 reviews) have been considered relevant for the purpose of this review.

Incidence

The incidence of perioperative stroke among patients who undergo noncardiovascular surgery is reported to be about 0.08–0.7% (0.3–0.4% symptomatic) [3, 4, 15, 16]. The incidence increases with age: 0.1–0.2% for age <65 years, 0.5% for age 65–74 years and 1.0% for age ≥75 years [3, 4, 17]. Perioperative mortality is remarkably high at 18–26% [3, 4, 15, 16].

Timing

The postoperative period is generally defined as 3–30 days after surgery, while most perioperative strokes are identified within the first days after surgery [1, 4–6].

Type of Surgery

The incidence of perioperative stroke depends on the type of the surgical procedure: 0.08–0.7% general surgery, 0.2–0.9% orthopedic surgery and 0.6–0.9% lung operations [3, 17–20]. Neck and head surgery have been associated with a high rate of perioperative stroke: 4.8% [21] (table 1). This high risk might be due to hyperextension and rotation leading to overstretching and compression of the neck’s major arteries that trigger intimal dissection, thrombus formation and vascular occlusion [1, 21]. Furthermore, this incidence is most likely underestimated as these patients typically have a tracheostomy in place; thus, communication is compromised and a neurological evaluation, especially in the presence of slight changes, is difficult to perform and the neurological deficit may easily be missed.

Causes and Pathophysiology

The main reported causes of perioperative ischemic stroke include cerebral atherothrombosis, lacunar stroke, cardioembolism due to atrial fibrillation (AF), dehydration, hypotension and perioperative systemic hypercoagulability [1, 4, 7, 22]. Other less common causes have been reported to be air, fat or paradoxical embolism and arterial dissection of neck arteries [18] (table 1). Perioperative strokes are predominantly ischemic and embolic rather than hemorrhagic [9, 10, 16]. New-onset AF is the comorbid diagnosis in 27.6% of postoperative stroke cases [3], leading to cardioembolism or cerebral hypoperfusion in those cases that develop a rapid ventricular response. Another cardiac source of emboli are diseased valves that can be favorable places for a thrombus to flourish because of alterations in blood flow coupled with perioperative hypercoagulability, hemodynamic changes and anticoagulation withholding [3].

Risk Factors

Patient-related risk factors include the following: age >70, female sex, previous stroke or transient ischemic attack, history of hypertension, diabetes mellitus, renal insufficiency, dialysis, smoking, chronic obstructive pulmonary disease, peripheral vascular disease, cardiac disease (history of myocardial infarction within 6 months prior to surgery, AF, valvular cardiopathy), carotid stenosis, atherosclerosis of the ascending aorta and the discontinuation of antithrombotic therapy before surgery. Procedure-related factors include timing of surgery (urgent vs. elective), type and duration of procedure, type of anesthesia (general vs. regional), intraoperative complications such as arrhythmia or heart rate alterations [23],

[1] Macellari/Paciaroni/Agnelli/Caso
hyperglycemia, dehydration and blood loss [18] (table 1). Particular attention is needed for those patients who have had previous stroke because they are at higher risk for perioperative cerebrovascular accidents [1, 2, 5–7, 11, 12, 19–21, 24–26]. In fact, general surgery has a low stroke risk of about 0.2% [19], but it increases to 2.9% in patients with precedent stroke [24] and rises to 3.6% in patients with carotid stenosis and prior symptoms [27]. If neurological symptoms are related to a basilar or intracranial vertebral artery stenosis, the perioperative stroke risk has been reported to be 6.0% with prolonged intraoperative hypotension acting as a precipitating factor [28]. The relation between asymptomatic carotid stenosis of any grade and the incidence of perioperative stroke in general elective surgery has not yet been determined [29].

**Anticoagulation Therapy before Surgery**

The management of patients taking oral anticoagulant (OAC) therapy is challenging because the risk of a thromboembolic event needs to be counterbalanced with the risk of bleeding. In a review of 31 reports on the perioperative treatment of patients receiving OAC, arterial thromboembolism and stroke rates were reported to be 1.6 and 0.4%, respectively, for all patients and 0.6 and 0.3%, respectively, for patients who had been taking warfarin therapy withheld without the administration of intravenous heparin or subcutaneous low-molecular-weight heparin (LMWH) [30]. On the other hand, an increase in major bleeding over the first 2 postoperative days has been reported to be approximately 2–4% for major surgery and 0–2% for invasive procedures [30]. Regarding new OAC agents, the risk of severe bleeding with dabigatran has been reported to be similar to that of patients using LMWH in orthopedic surgery, and the same as or lower than patients with well-controlled AF on warfarin (3.11 vs. 3.36%, respectively) [31]. Despite the clinical indication, patients with AF are frequently not put back on anticoagulation after surgery.

**Antiplatelet Withdrawal before Surgery**

Due to the high incidence of cardiovascular disease, antiplatelets are widely prescribed to up to 25% of the elderly population under aspirin (acetylsalicylic acid, ASA) treatment [32]. Antiplatelet drugs are effective in preventing arterial thrombosis both in primary [33, 34] and secondary [35] prevention but their continuation could lead to bleeding in the operative setting. This risk depends on the type of therapy (one, two or more antiplatelet drugs), surgical procedure (hip arthroplasty, tonsillectomy and transurethral resection of the prostate tend to bleed more; neurosurgery, ophthalmology and otorhinolaryngology

<table>
<thead>
<tr>
<th>Causes</th>
<th>Risk factors with odds ratios [3, 4, 17, 18, 23]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral atherothrombosis</td>
<td>23.6 (9.6–58.1) [17]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.2 (1.25–1.62) [3]</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>5.36 (4.68–6.13) [3]</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1.61 (1.44–1.81) [3]</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.20 (1.77–2.74) [3]</td>
</tr>
<tr>
<td>Perioperative systemic hypercoagulability</td>
<td>3.98 (3.57–4.45) [3]</td>
</tr>
<tr>
<td>Paradoxical embolism</td>
<td>5.5 (2.8–10.9) [17]</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>3.71 (3.26–4.22) [3]</td>
</tr>
<tr>
<td>Risk factors with odds ratios [3, 4, 17, 18, 23]</td>
<td>2.51 (2.10–2.99) [3]</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>1.75 (1.56–1.97) [3]</td>
</tr>
<tr>
<td>Previous stroke or transient ischemic attack</td>
<td>2.2 (1.3–4.1) [17]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.2 (1.4–3.3) [17]</td>
</tr>
<tr>
<td>Renal insufficiency and dialysis</td>
<td>2.20 (1.77–2.74) [3]</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3.71 (3.26–4.22) [3]</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.51 (2.10–2.99) [3]</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.75 (1.56–1.97) [3]</td>
</tr>
<tr>
<td>AF</td>
<td>2.20 (1.77–2.74) [3]</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.51 (2.10–2.99) [3]</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>3.71 (3.26–4.22) [3]</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.3 (1.3–4.1) [17]</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2.5 (1.4–4.4)</td>
</tr>
</tbody>
</table>

**Other risk factors**

- Female sex
- Hypertension
- Smoking
- Carotid stenosis
- Atherosclerosis of the ascending aorta
- Discontinuation of antithrombotic therapy before surgery
- Timing of surgery (urgent vs. elective)
- Type and duration of procedure
- Type of anesthesia (general vs. regional)
- Intraoperative complications (arrhythmia or heart rate alterations)
- Hyperglycemia
- Dehydration
- Blood loss

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Risk factors with odds ratios [3, 17–21, 26, 57]</th>
</tr>
</thead>
<tbody>
<tr>
<td>General (0.08–0.7%) [3, 26]</td>
<td>23.6 (9.6–58.1) [17]</td>
</tr>
<tr>
<td>Orthopedic (0.2–0.9%) [3, 20]</td>
<td>1.2 (1.25–1.62) [3]</td>
</tr>
<tr>
<td>Lung (0.6–0.9%) [3, 17]</td>
<td>5.36 (4.68–6.13) [3]</td>
</tr>
<tr>
<td>Peripheral vascular (0.3–3%) [18, 20]</td>
<td>1.61 (1.44–1.81) [3]</td>
</tr>
<tr>
<td>Neck and head (3.2–4.8%) [21, 57]</td>
<td>2.20 (1.77–2.74) [3]</td>
</tr>
</tbody>
</table>

For risk factors, values in parentheses are 95% confidence intervals; for type of surgery, percent incidence is given in parentheses; the incidence is expressed as a range using the minimum and the maximum values described in the literature.

* Neck dissection and simultaneous carotid endarterectomy.

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do not permit even minimal bleeding) and the sensitivity of patients to antiplatelet agents [36]. Patients taking ASA have a 1.5-fold higher risk of blood loss without any increase in bleeding-related surgical mortality or morbidity [37]. Thus, low-dose ASA increases bleeding only quantitatively and does not move the bleeding complications toward a higher risk quality [37]. In fact, for anatomical reasons, urological interventions and diagnostic procedures tend to have a high rate of bleeding. In addition, a randomized controlled study has reported that there was no difference in intraoperative hemorrhage, operation time and amount of tissue resected between patients taking ASA during transurethral resection of the prostate and those not taking ASA, even though there was a reported increase in postoperative blood loss of 51% (284 vs. 144 ml) [38].

Regarding clopidogrel, only a limited number of case reports and a small clinical series of visceral and vascular surgery have been published. However, a recent study has reported that patients receiving clopidogrel 5 days before lung resection had similar mortality, postoperative length of stay, rate of perioperative transfusion, reoperation for bleeding, myocardial infarction and stroke compared to controls sharing the same risk factors for both thrombosis and increased blood loss [39]. Thus, withdrawing clopidogrel only 5 days instead of 7–10 days [40] before major surgery seems to be safe and allows for adequate hemostasis. Clopidogrel plus ASA increases surgical bleeding and the rate of transfusion by 50% without increasing morbidity, mortality or surgical outcome [41]. Nevertheless, this type of bleeding is rarely life threatening and can be managed like any other type and even prevented by using less invasive or advanced surgical approaches [42].

The abrupt discontinuation of antiplatelet agents, in fact, is associated with a rebound phenomenon that accentuates the problem and makes the thrombus formation more probable [43]. The time interval between discontinuation and acute cerebral events has been reported to be 14.3 ± 11.3 days [37]. Despite the high thrombotic risk, of 287 English urologists, 62% withdrew ASA prior to transurethral resection of the prostate without specifying any reason [44]. Additionally, an American survey of ophthalmologists found that 52% discontinued ASA prior to surgery, while a survey of gastroenterologists reported that 81% stopped ASA before colonoscopy, 79% before endoscopic retrograde cholangiopancreatography and 51% prior to upper endoscopy [45, 46].

Conclusions

Even if the incidence of perioperative stroke among patients who undergo noncardiovascular surgery is reported to be very low (0.3–0.4% symptomatic) [3, 4, 15,
16), it nonetheless remains a devastating disease with a high perioperative mortality (18–26%) [3, 4, 15, 16]. Management guidelines for patients with vascular disease undergoing surgery are insufficient and, therefore, surgeons generally make these decisions independently. On the basis of the findings of this review, the authors make the following recommendations (table 2).

Regarding symptomatic stenosis ≥70%, carotid revascularization by carotid endarterectomy or carotid artery stenting before general surgery is the standard care [47], while there is no evidence to date to support a prophylactic revascularization in asymptomatic patients that would expose them to a 2-fold higher risk of perioperative stroke and myocardial infarction without significantly reducing the risk of stroke [48–50]. However, of these latter patients, those having hemodynamically significant bilateral carotid stenosis may benefit from revascularization [18].

The guidelines of the American College of Chest Physicians (ACCP) recommend stopping OACs approximately 5 days before major surgery to adequately allow the INR to normalize and, at the same time, to start the ‘bridging anticoagulation’ with subcutaneous LMWH or intravenous unfractionated heparin (UFH) at different dosages (therapeutic or prophylactic) and different timings depending on the individual thrombotic risk of the patient [40]. Specifically, as far as bridging therapy is concerned, the last dose of LMWH must be given no less than 12 h before the operation with a twice-daily regimen, or 24 h before the operation with a once-daily regimen to avoid the persistence of anticoagulant effect during surgery [51]. If intravenous UFH has been used, it should be stopped 4–6 h prior to surgery. OACs must be resumed 12–24 h after surgery together with heparin, as warfarin takes a few days to reach its full effect [40]. Regarding new anticoagulants, dabigatran does not need to be withheld for minor procedures, whereas for major surgery it has to be discontinued 24 h to 5 days prior to surgery depending on the risk of bleeding and on the renal function of the patient. Dabigatran can be resumed 1–4 h after surgery if the wound is stable, otherwise the resumption must be delayed. If the patient has a high thrombotic risk a perioperative bridging therapy with heparin should be considered. Currently, there are no clear recommendations on the use of rivaroxaban and apixaban.

Data concerning the management of patients undergoing antiplatelet therapy are lacking. To date, the ACCP guidelines discourage the perioperative withdrawal of ASA, especially in patients in secondary prevention [40]. If the interruption is absolutely needed, resumption within 24 h after the procedure is suggested [40]. When clopidogrel withdrawal is required in order to reduce perioperative bleeding, bridging therapy, which includes short-acting intravenous glycoprotein IIb/IIIa inhibitors such as tirofiban or eptifibatide (until just before intervention in those patients with coronary stent recently implanted), can be administered [52, 53]. The ACCP guidelines suggest against the routine use of bridging therapy with UFH or LMWH because the efficacy and safety data on patients taking antiplatelet therapy are lacking [40]. In fact, heparin does not have antiplatelet properties and is not protective against stent thrombosis [54, 55]. Despite this, many surgeons substitute antiplatelet therapy with LMWH as an antithrombotic bridging therapy or, empirically, use the same doses of the venous thromboembolism prophylaxis.

The Antiplatelet Agents in the Perioperative Management of Patients Trial, an ongoing randomized controlled trial, has the aim of assessing the safety and determining the optimal use of ASA in the perioperative management of patients undergoing general and abdominal surgery. This is being done by comparing a group of low-risk patients, who were withdrawn from ASA 5 days prior to surgery and resumed taking it 5 days after the intervention, to controls who did not discontinue the antiplatelet agent [56].

While waiting upon the results of the above-mentioned and other trials, an individualized, accurate, multidisciplinary (surgical, neurological, cardiological and anesthesiological) risk/benefit assessment remains the best basis for treatment decision.

References


