Epidural analgesia in vascular surgery patients actively taking clopidogrel

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The administration of anti-platelet agents to surgical patients with a history of coronary artery disease or peripheral vascular disease represents an everyday challenge to anaesthesiologists when epidural anaesthesia or analgesia is to be considered. Practice guidelines suggest stopping clopidogrel at least 7 days before placing an epidural catheter. Withholding anti-platelet drugs represents a great risk to many of these patients. On the other hand, withholding perioperative epidural analgesia denies the patients its benefits including faster resolution of postoperative ileus, earlier ambulation, decreased risk of thromboembolism and vascular graft thrombosis, and decreased hospital stay. The charts of 306 vascular surgical patients who received epidural analgesia without withholding clopidogrel perioperatively were reviewed for the presence of any postoperative complications related to the continued intake of clopidogrel. No postoperative neurological complications resulting from the use of epidural analgesia were found in any of these patients. The point estimate (95% confidence limits) for the risk of epidural hematoma or other complications for this study is 0 (0–1)%. No neurological complications were found as a result of placing an epidural catheter in patients actively taking clopidogrel. Owing to the small sample size, we cannot recommend the liberal use of epidural analgesia with ongoing clopidogrel administration at this time. Further prospective studies, with larger sample size, are needed in order to substantiate our findings.

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The increasing use of anti-platelet agents in surgical patients with a history of coronary artery disease, peripheral vascular disease, or ischaemic strokes represents an everyday challenge to anaesthesiologists when epidural anaesthesia or analgesia is being considered. A growing number of patients undergoing coronary and vascular angioplasty with stenting receive anti-platelet medications (APMs) in order to prevent acute thrombotic events or stent occlusion.1–3 Other life-threatening medical conditions such as congestive heart failure, ischaemic cerebrovascular disease, retinal artery occlusion, and peripheral vascular disease also necessitate the use of APMs. Clopidogrel is an APM that is being increasingly used for the secondary prevention of such conditions. It is a thienopyridine derivative that exerts its anti-platelet effect by binding irreversibly to the adenosine diphosphate receptors on the surface of platelets.4 APMs, including clopidogrel, are known to increase the risk of surgical bleeding, and it is a common practice to stop such medications at least 7–10 days before any surgery.5 Epidural haematoma is a rare but potentially devastating complication of neuraxial block. There is little information on the risk of such a complication in patients who received epidural anaesthesia or analgesia while taking clopidogrel. Current recommendations from the American Society of Regional Anesthesia (ASRA) consensus conference suggest that clopidogrel should be stopped at least 7 days before any form of neuraxial block.5 However, the abrupt cessation of APMs, in particular clopidogrel, is a major independent risk factor for serious morbidities such as stroke and coronary stent occlusion leading to myocardial infarction; this is especially true in the perioperative period.6 On the other hand, withholding perioperative epidural analgesia may deny the patients the reported benefits of this procedure, including faster resolution of postoperative ileus, earlier ambulation, decreased risk of thromboembolism and
vascular graft thrombosis, and decreased hospital stay.\(^7\)\(^8\) In this paper, we report the outcome of more than 300 patients who received epidural analgesia while taking clopidogrel during the entire perioperative period.

**Methods**

Over the period 2001 and 2006, a physician team at our institution decided, based on their clinical judgement, to offer epidural analgesia to a series of vascular surgical patients who were taking clopidogrel, after obtaining the usual clinical consent from each patient and without withholding that medication perioperatively. The patients who were considered for epidural analgesia while taking clopidogrel were those who were undergoing an elective lower extremity revascularization or amputation surgery, were on the regular operating room (OR) schedule, and were haemodynamically stable. No emergency cases were considered. All participating patients understood the risks and benefits of placing the epidural catheter while actively taking clopidogrel and they agreed to proceed. Clopidogrel was withheld on the day of the surgery only (due to the preoperative *non per os* or NPO status) and was restarted on postoperative day 1 as per the surgeon request. On the day of the surgery, a 20 G epidural catheter was placed in all patients before operation and was kept for 2–3 days, depending on the anticipated day of discharge. An 18 G Tuohy needle was used to place the catheter in the lumbar–midline spinal area. If there was no success in placing the catheter after two attempts, the procedure was aborted. If a bloody tap was obtained, the procedure was aborted. After operation, all patients with attempted placement of an epidural catheter (successfully or unsuccessfully including those who had a bloody tap) received neurological checks every 2 h in the first 24 h and then every 4–6 h for the next 72 h or until discharge whichever comes first. The neurological monitoring included checking for new back pain, lower extremity numbness or weakness, and bowel or urinary incontinence. All catheters were removed by postoperative day 3. The epidural solution included a local anaesthetic and either fentanyl or hydromorphone. The exact composition of the solution was patient-specific and was tailored to the patient’s condition and tolerance to narcotics. All information regarding the placement of the epidural catheter, including the catheter size, number of attempts, and block level, were recorded in detail on the chart.

Institutional Review Board approval was obtained to review the medical records of these patients for the presence of any perioperative complication that might be attributed to the provision of epidural analgesia. Information gathered about these patients included age, sex, race, medications (besides clopidogrel), and comorbidities including hypertension (on anti-hypertensive medications), diabetes (on oral hypoglycaemic medications or insulin), coronary artery disease (radiographic evidence of coronary artery narrowing or myocardial dysfunction, history of myocardial infarct, or history of coronary artery revascularization), and congestive heart failure (systolic ejection fraction <45% on echocardiography). We subsequently looked for documentation of new neurological symptoms (numbness, weakness, paralysis, tingling, bowel incontinence, and urinary incontinence) or radiologically proven evidence of epidural haematoma in the first 3 months after operation.

Estimates of the upper limit of confidence interval for the risk of epidural haematoma or other complications after the placement of the epidural catheter was calculated using the formula \(3/n\), where \(n\) is the number of patients in which no complications were found.\(^9\)

**Results**

All vascular surgical patients who received epidural analgesia without withholding clopidogrel perioperatively between the years 2001 and 2006 were included in this study. The total number was 306 patients. Two hundred and eighty-two patients (92%) were from the African American community. This is due to the fact that our medical centre mainly serves the African American community of Detroit, MI, USA. Of those, 205 (67%) were males and 77 (25%) were females. The remaining patients (24 patients or 8% of patients) were White Caucasians. Of those, 19 (6%) were males and five (2%) were females. The age of patients ranged between 49 and 74 yr with a median of 61 yr. All the patients were undergoing a vascular surgical procedure. These 306 patients represent only a small fraction of the total number of patients who underwent vascular surgeries while taking clopidogrel in our medical centre which performs more than 1000 vascular operations a year, the majority of which are on patients taking clopidogrel. Two hundred and seventeen patients (71%) underwent lower extremity vascular bypass surgery, including axillary–femoral, femoral–femoral, and femoral–politeal bypasses. The remainder underwent a lower extremity amputation. All these patients were taking clopidogrel before operation for their history of peripheral vascular disease. Most patients had comorbidities including hypertension, diabetes mellitus, coronary artery disease, and other diseases (Table 1). Of the 306 patients, 217 were

<table>
<thead>
<tr>
<th>Coexisting conditions</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral vascular disease</td>
<td>306 (100)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>274 (89)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>89 (29)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>162 (53)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>39 (13)</td>
</tr>
<tr>
<td>History of cerebrovascular accidents</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>65 (21)</td>
</tr>
</tbody>
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also on aspirin 81 mg daily which was continued through the perioperative period, and 238 received an intraoperative dose of i.v. heparin (5000 units) which was not reversed at the end of the surgery. We also identified three patients who had a bloody tap as a result of which the placement of an epidural catheter was aborted. None of the 306 patients who had an epidural catheter placed or the three patients who had a bloody tap developed any new neurological symptoms or other clinical evidence of epidural haematoma. None of these patients developed any new symptoms that required the performance of radiological studies such as MRI. Many of these patients had baseline neurological deficits secondary to peripheral neuropathy, strokes, or other comorbidities. However, our chart review did not note any worsening of such symptoms or any development of new deficits in these patients.

No complications related to the attempted procedure were noted up to the date of discharge, which is not sooner than postoperative day 3 for all the vascular surgery procedures considered in this study. For our sample size of 306 patients, the point estimate (95% confidence limits) for the risk of epidural haematoma or other complications is 0 (0–1)%.

Discussion

Despite being extremely rare, the development of epidural haematoma is a known risk after epidural analgesia whether or not the patient is taking APMs. The third National Audit Project (NAP3) of the Royal College of Anaesthetists found an incidence of five cases of epidural haematoma for 293,000 epidurals performed or about two in 100,000 cases. The incidence of spontaneous epidural haematoma is rarer, estimated at 1 per 1,000,000 patients per year, most going undetected. Several other factors, such as advanced age, female gender, bony spinal pathology that may necessitate multiple attempts, and cougulopathy, also increase the risk of patients developing an epidural haematoma after epidural block.

Antiplatelet agents are known to be protective in most patients at increased risk of occlusive vascular events, including those with an acute myocardial infarction, ischaemic stroke, angina, peripheral arterial disease, or atrial fibrillation. Specifically, it has been shown that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is effective in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death, more than aspirin. Two recent studies found that the risk of surgical bleeding is not significantly associated with the intake of APMs.

The ASA closed claims project showed that the highest risk for spinal haematoma was in patients receiving neuraxial block in combination with heparin infusion. There are no data suggesting the increased risk with the addition of clopidogrel. Current ASRA recommendations to stop clopidogrel 7 days before the surgery are based on level III evidence such as clinical judgement and sporadic case reports of epidural haematoma after spinal analgesia, combined spinal–epidural analgesia, or both in patients with a history of taking clopidogrel in combination with other anticoagulants. This would place the ASRA recommendations in the level C category according to the US Preventive Services Task Force classification. To date, no prospective studies have investigated the safety of epidural analgesia in patients actively taking clopidogrel. Our chart review did not show any increase in the incidence of clinically significant spinal bleeding and neurological complications after epidural analgesia while actively taking clopidogrel, although the number of patients who received this treatment was small. This remained true despite the fact that 78% of our patients received intraoperative i.v. heparin and 217 (71%) were also on aspirin 81 mg daily. At least one other study has reported the absence of complications after peripheral non-neuraxial blocks in patients actively taking clopidogrel.

However, we feel that our data should be interpreted with caution. We studied a small sample of 306 patients. The upper limit of the confidence interval for the incidence of epidural haematoma is about 1% which is high when compared with the 2 per 100,000 reported by the NAP3. A much higher sample size, probably in the order of 200,000, would be required in order to confirm a similar incidence of epidural haematoma to that reported in the NAP3 audit.

Given the small sample size in our review, we cannot recommend the liberal use of epidural analgesia in patients actively taking clopidogrel. We recognize that the outcome might be different with a bigger sample size. The fact that, over a period of 6 yr, only 306 patients received epidural analgesia, in a medical centre that performs more than 1000 vascular surgeries a year, underlines the fact that this practice is not suitable for everybody and that not all patients were willing to take the extra risk. Nevertheless, our data may constitute a basis for larger prospective studies or retrospective meta-analysis where the accurate incidence of complications will be delineated.

Regardless of whether the patient is receiving clopidogrel or not, it is very important to look for signs and symptoms of epidural bleeding and to diagnose it early on, so that treatment can be initiated promptly. Successful neurological recovery after evacuation of a spinal haematoma depends on the interval between onset of symptoms and timing of surgery with best outcome if the patient is operated on within 8 h of developing symptoms.

Our chart review of 306 patients did not reveal any clinically significant complication resulting from the use of epidural analgesia in vascular surgery patients who are taking clopidogrel. This report is not meant to recommend the liberal placement of epidural catheters in patients actively taking clopidogrel. However, for certain high-risk patients,
the benefit of placing an epidural catheter while actively taking clopidogrel may be considered. Randomized, controlled, prospective studies with a large number of patients are needed in order to give more accurate recommendation regarding performing epidural block in patients actively taking clopidogrel.

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**References**