Sellar and parasellar tumor removal without discontinuing antithrombotic therapy

Yoshikazu Ogawa, MD, PhD,¹ and Teiji Tominaga, MD, PhD²

¹Department of Neurosurgery, Kohnan Hospital; and ²Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

OBJECT Treatment with dual antiplatelet agents associated with coronary stenting procedures and long-term anticoagulant therapy is increasingly common, but the treatment carries risks during surgical procedures. Evidence-based recommendations have proposed discontinuation of antithrombotic treatment or introduction of bridging therapy in some procedures less invasive and with lower risk of bleeding. However, neurosurgical procedures without discontinuation of antithrombotic treatment and perioperative management have received little investigation.

METHODS Between October 2008 and January 2014, 15 consecutive patients (11 males and 4 females; age range 51–75 years [mean 68.2 years]), with sellar and parasellar tumors were treated through the transsphenoidal approach without discontinuation of antithrombotic therapy. Clinical data were compared with another 15 patients, who underwent transsphenoidal surgeries without preoperative antithrombotic therapy.

RESULTS Gross-total removal of the tumor or total aspiration of the content of Rathke’s cleft cyst was achieved in 13 patients, and subtotal removal was achieved in 1 patient with a small remnant in the cavernous sinus. No difference was found in intraoperative bleeding between the antithrombotic agent group and the control group (mean 255 ml vs 215 ml, Mann-Whitney U-test, p = 0.547), and no patient required transfusion. No difference was found in operation time between the antithrombotic agent group and the control group (167.8 minutes vs 150.0 minutes, Mann-Whitney U-test, p = 0.262). All patients were discharged on postoperative Day 12 without neurological deficits.

CONCLUSIONS The present study suggests that discontinuation of antithrombotic therapy may be unnecessary before the typical transsphenoidal surgery. Large randomized clinical trials at multiple centers are needed to confirm these findings.

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KEY WORDS anticoagulant; antiplatelet; antithrombotic therapy; discontinuation; operation; transsphenoidal approach; pituitary surgery

Long-term anticoagulant therapy is currently administered to more than 6 million patients for the treatment of atrial fibrillation, deep venous thrombosis, various valve diseases, and malignancy-related syndromes. In addition, recent advances in coronary stenting procedures have rapidly increased the need for treatment with dual antiplatelet agents. However, about 10% of these patients will undergo invasive procedures every year, which will require temporary discontinuation of the antithrombotic therapy or some bridging therapy. Evidence-based recommendations have been proposed to deal with this complicated countermeasure in some less invasive procedures with lower risk of bleeding, such as dental procedures or cataract operations.

However, procedures without discontinuation of antithrombotic treatment have received little attention, and the perioperative period in neurosurgical procedures has also been less well studied.

The present clinical study retrospectively analyzed a series of transsphenoidal surgeries performed without discontinuation of antithrombotic therapy for comparison with the same number of transsphenoidal surgeries performed in the absence of antithrombotic therapy.

Methods

Between October 2008 and January 2014, 15 consecutive patients (11 males and 4 females; age range 51–75
were treated via a transsphenoidal approach by a single surgeon (Y.O.), accounting for 2.51% of all transsphe-
nowal operations during the same period. The histological
diagnoses were pituitary adenoma (n = 9), Rathke’s
cleft cyst (n = 4), clival chordoma (n = 1), and biopsy of
skull base pachymeningitis (n = 1). Eleven patients were
treated with antplatelet agents and 4 with anticoagulant
agents. The prothrombin time–international normalized
ratio (PT-INR) was measured preoperatively before ad-
ministering anticoagulant agents, which verified that all
PT-INRs were within the required limits (Table 1). The
patients continued to take antithrombotic agents until the
morning of surgery, and, after verification of the absence
of ischemic and/or hemorrhagic complications on the
morning of postoperative Day 1, administration of anti-
thrombotic agents was restarted. All operations were
performed via sublabial mucosal incisions, and the closest
attention was paid to preserve the arachnoid plane at the top
of the lesions in expectation of postprocedural hemostasis
by compressive pressure of CSF spaces. Extended trans-
sphenoidal surgeries through the subarachnoid spaces
and giant pituitary adenomas with a maximum diameter
larger than 40 mm were excluded due to the presumptive
high risk of after-bleeding. Clinical data were compared
with the data of 15 patients who underwent transsphenoi-
dal surgery without preoperative antithrombotic therapy
between December 2013 and January 2014. The surgical
policy was explained preoperatively to the patients, and
written informed consent was obtained. The overall study
design was approved by the ethics committee of Kohnan
Hospital. Statistical comparisons used Mini Statmate soft-
ware (ATMS Co., Ltd.), and p values < 0.05 were regarded
as significant.

Results

Gross-total removal of the tumor or total aspiration of
the content of the Rathke’s cleft cyst was achieved in 13
patients, and subtotal removal was achieved in 1 patient
with a small remnant in the cavernous sinus. Aggressive
removal was suspended in 1 patient because intraoperative
histological examination had revealed pachymeningitis.
Head CT scanning performed the morning of postopera-
tive Day 1 revealed that most cavities of the sellae were
occupied with CSF, so-called empty sellae. No patient
experienced massive abnormal bleeding throughout the
hospital course. Comparison of the antithrombotic agent
group and the control group found no difference in preop-
erative tumor volume (antithrombotic agent group vs con-
trol: 2.45 ml vs 3.18 ml, p = 0.48), but patients were older
in the antithrombotic agent group (63.32 years vs 57.73
years, p = 0.029). Opening of the ipsilateral cavernous
sinus occurred in 4 patients in the antithrombotic agent
group, but hemostasis was achieved in all patients with
common techniques, such as compression with cotton
flakes and/or point-by-point coagulation. In the antithrom-
botic agent group, bleeding varied from 100 ml to 485 ml
(mean 255 ml), and no patient required transfusion, even
after open cavernous sinus surgeries. Comparison of the
antithrombotic agent group and the control group found
no difference in intraoperative bleeding (255 ml vs 215
ml, Mann-Whitney U-test, p = 0.547). Operation time var-
ed in the antithrombotic agent group from 114 minutes
to 241 minutes (mean 167.8 minutes). Comparison of the
antithrombotic agent group and the control group found
no difference in operation time (167.8 minutes vs 150.0
minutes, Mann-Whitney U-test, p = 0.262) (Tables 2 and
3). All patients were discharged on postoperative Day 12
without neurological deficits.

TABLE 1. Profiles of patients undergoing antithrombotic therapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Histology</th>
<th>Antithrombotic Agent</th>
<th>Reason</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74, M</td>
<td>Atypical adenoma</td>
<td>Aspirin 100 mg</td>
<td>ACA stenosis</td>
<td>Opening of CS</td>
</tr>
<tr>
<td>2</td>
<td>67, M</td>
<td>Rathke’s cleft cyst</td>
<td>Aspirin 100 mg</td>
<td>Coronary stent</td>
<td>Opening of CS</td>
</tr>
<tr>
<td>3</td>
<td>75, M</td>
<td>Plurihormonal adenoma</td>
<td>Aspirin 100 mg</td>
<td>Angina</td>
<td>Opening of CS</td>
</tr>
<tr>
<td>4</td>
<td>71, F</td>
<td>Rathke’s cleft cyst</td>
<td>Clopidogrel 25 mg</td>
<td>MCA stenosis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>72, M</td>
<td>Rathke’s cleft cyst</td>
<td>Aspirin 81 mg</td>
<td>AMI</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>75, F</td>
<td>Acromegaly</td>
<td>PT-INR 1.34</td>
<td>Paroxysmal AF</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>62, M</td>
<td>Plurihormonal adenoma</td>
<td>Aspirin 100 mg</td>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>66, M</td>
<td>Rathke’s cleft cyst</td>
<td>Aspirin 100 mg</td>
<td>Coronary stent</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>67, F</td>
<td>Gonadotroph cell adenoma</td>
<td>Ticlopidine 200 mg</td>
<td>Y graft &amp; FF bypass</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>72, M</td>
<td>Mixed GH &amp; PRL adenoma</td>
<td>Cilostazol 200 mg</td>
<td>Aortic dissection</td>
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<tr>
<td>11</td>
<td>51, M</td>
<td>Pachymeningitis</td>
<td>PT-INR 2.01</td>
<td>AVR, AV block (3)</td>
<td>Temporary pacemaker</td>
</tr>
<tr>
<td>12</td>
<td>69, M</td>
<td>Plurihormonal adenoma</td>
<td>Aspirin 100 mg</td>
<td>Coronary stent</td>
<td>Opening of CS</td>
</tr>
<tr>
<td>13</td>
<td>70, M</td>
<td>Null cell adenoma</td>
<td>Aspirin 100 mg</td>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>71, F</td>
<td>Corticotroph cell adenoma</td>
<td>PT-INR 1.55</td>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>61, M</td>
<td>Chordoma</td>
<td>PT-INR 1.95</td>
<td>Paroxysmal AF</td>
<td>Opening of CS</td>
</tr>
</tbody>
</table>

ACA = anterior cerebral artery; AF = atrial fibrillation; AMI = acute myocardial infarction; AV = atrioventricular; AVR = aortic valve replacement; CS = cavernous sinus; DVT = deep venous thrombosis; FF = femoral-femoral; GH = growth hormone; MCA = middle cerebral artery; PRL = prolactin; PT-INR = prothrombin time–international normalized ratio.
Discussion

The risk of thrombosis has been estimated for some systemic diseases or conditions. Recent venous thrombosis (within 1 month), repeated arteriovenous thrombophilia, and mitral valve disease carry higher risks of thrombosis, whereas old venous thrombosis (> 3 months) and nonvalvular atrial fibrillation involve lower risks of thrombosis. Invasive procedures also involve the risk of bleeding in patients receiving antithrombotic therapy. Orthopedic hip procedures and colon polypectomy have higher risks of bleeding, whereas dental procedures, cataract surgery, dermatological procedures, and surgery for carpal tunnel syndrome have lower risks of bleeding. The factors of thrombogenesis and fibrinolysis have been specifically considered in some invasive procedures, resulting in evidence-based recommendations for discontinuation of antithrombotic therapy or introduction of bridging therapy. A large randomized study was reported recently in patients receiving or not receiving aspirin therapy who underwent noncardiac surgery. The study revealed that there was not an increase in cardiac or cerebrovascular events in the patients who discontinued the antiplatelet therapy compared with those who did not, although there was a slight increase in the amount of hemorrhage in the group that stayed on antiplatelet therapy. However, in this study more than two-thirds of the patients had received bridging anticoagulant therapy, so the true result with or without discontinuation of antiplatelet therapy in perioperative period remains unsolved.

Very few clinical studies have considered perioperative management of neurosurgical patients receiving antithrombotic therapy except for antiplatelet therapies incorporated in intravascular treatments. Temporary discontinuation of antithrombotic therapy or introduction

<p>| TABLE 2. Results of surgery with antithrombotic therapy |
|----------------|-----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Histology</th>
<th>Vol (ml)</th>
<th>Blood Loss (ml)</th>
<th>Operation Time (mins)</th>
<th>Removal Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atypical adenoma</td>
<td>1.89</td>
<td>130</td>
<td>164</td>
<td>100</td>
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<tr>
<td>2</td>
<td>Rathke’s cleft cyst</td>
<td>0.86</td>
<td>230</td>
<td>114</td>
<td>100</td>
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<tr>
<td>3</td>
<td>Plurihormonal adenoma</td>
<td>1.16</td>
<td>125</td>
<td>149</td>
<td>100</td>
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<td>4</td>
<td>Rathke’s cleft cyst</td>
<td>0.94</td>
<td>485</td>
<td>162</td>
<td>100</td>
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<td>5</td>
<td>Rathke’s cleft cyst</td>
<td>0.09</td>
<td>100</td>
<td>137</td>
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<td>6</td>
<td>Acromegaly</td>
<td>3.04</td>
<td>150</td>
<td>127</td>
<td>100</td>
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<td>7</td>
<td>Plurihormonal adenoma</td>
<td>4.39</td>
<td>290</td>
<td>228</td>
<td>100</td>
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<tr>
<td>8</td>
<td>Rathke’s cleft cyst</td>
<td>0.5</td>
<td>125</td>
<td>123</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>Gonadotroph cell adenoma</td>
<td>0.6</td>
<td>300</td>
<td>144</td>
<td>100</td>
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<tr>
<td>10</td>
<td>Mixed GH &amp; PRL adenoma</td>
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<td>460</td>
<td>171</td>
<td>100</td>
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<tr>
<td>11</td>
<td>Pachymeningitis</td>
<td>115</td>
<td>241</td>
<td>Biopsy</td>
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<tr>
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<td>Plurihormonal adenoma</td>
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<td>425</td>
<td>237</td>
<td>96</td>
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<tr>
<td>13</td>
<td>Null cell adenoma</td>
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<td>205</td>
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<td>100</td>
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<tr>
<td>14</td>
<td>Corticotroph cell adenoma</td>
<td>0.01</td>
<td>290</td>
<td>195</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>Chordoma</td>
<td>3.4</td>
<td>400</td>
<td>194</td>
<td>100</td>
</tr>
</tbody>
</table>

<p>| TABLE 3. Results of surgery without antithrombotic therapy |
|----------------|-----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Pathology</th>
<th>Vol (ml)</th>
<th>Blood Loss (ml)</th>
<th>Operation Time (mins)</th>
<th>Removal Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>28, F</td>
<td>Lactotroph cell adenoma</td>
<td>0.05</td>
<td>135</td>
<td>156</td>
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<td>17</td>
<td>54, F</td>
<td>Acromegaly</td>
<td>4.82</td>
<td>245</td>
<td>199</td>
<td>98</td>
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<tr>
<td>18</td>
<td>58, M</td>
<td>Nonfunctioning</td>
<td>1.89</td>
<td>185</td>
<td>147</td>
<td>100</td>
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<tr>
<td>19</td>
<td>46, M</td>
<td>Plurihormonal adenoma</td>
<td>3.56</td>
<td>150</td>
<td>164</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>71, F</td>
<td>Plurihormonal adenoma</td>
<td>2.28</td>
<td>163</td>
<td>157</td>
<td>100</td>
</tr>
<tr>
<td>21</td>
<td>41, M</td>
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<td>2.57</td>
<td>134</td>
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<td>100</td>
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<tr>
<td>22</td>
<td>65, F</td>
<td>Plurihormonal adenoma</td>
<td>0.91</td>
<td>353</td>
<td>145</td>
<td>100</td>
</tr>
<tr>
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<td>66, M</td>
<td>Plurihormonal adenoma</td>
<td>3.23</td>
<td>345</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
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<td>180</td>
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<td>100</td>
</tr>
<tr>
<td>25</td>
<td>62, F</td>
<td>Mixed GH &amp; PRL adenoma</td>
<td>0.32</td>
<td>100</td>
<td>119</td>
<td>100</td>
</tr>
<tr>
<td>26</td>
<td>70, M</td>
<td>Plurihormonal adenoma</td>
<td>5.86</td>
<td>350</td>
<td>191</td>
<td>100</td>
</tr>
<tr>
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<td>81, M</td>
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<td>100</td>
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<tr>
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<td>Somatotroph cell adenoma</td>
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<td>190</td>
<td>95</td>
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<td>148</td>
<td>100</td>
</tr>
<tr>
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<td>Plurihormonal adenoma</td>
<td>0.19</td>
<td>100</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>
of bridging therapy is rarely mentioned in cases of internal carotid artery dissection,\textsuperscript{40} as is placement of cutaneous-ventricular drainage for patients after intravascular treatment.\textsuperscript{41} However, these cases do not provide a high level of medical evidence.

The present cohort study was performed at a single institution and by a single surgeon. The protocol was simple, as neither discontinuation of antithrombotic therapy nor introduction of bridging therapy was required. Therefore, the treatment and control groups were easily compared. However, the true implications cannot be fully clarified, and validation of this protocol is limited only to extraarachnoid, typical transsphenoidal surgeries. Large randomized clinical trials at multiple centers are essential to recommend standardization of this management for patients receiving antithrombotic therapy. Although patients receiving antithrombotic therapy should only undergo transsphenoidal surgery when absolutely necessary, various types of procedures should be investigated to establish a high level of medical evidence about this increasing problem in the neurosurgical field.

Conclusions

Transsphenoidal surgeries were performed in 15 patients without discontinuation of antithrombotic therapy. No patient required transfusion, and intraoperative bleeding, operation time, and tumor removal rate showed no significant differences between these patients and the control group. The present study suggests that discontinuation of antithrombotic therapy may be unnecessary before the typical transsphenoidal surgery. Large randomized clinical trials are needed to establish validation of this procedure.

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Author Contributions
Conception and design: Ogawa. Acquisition of data: Ogawa. Analysis and interpretation of data: Ogawa. Drafting the article: Ogawa. Critically revising the article: both authors. Reviewed submitted version of manuscript: Tominaga. Approved the final version of the manuscript on behalf of both authors: Ogawa. Statistical analysis: Ogawa. Administrative/technical/material support: Ogawa. Study supervision: Tominaga.

Correspondence
Yoshikazu Ogawa, Department of Neurosurgery, Kohnan Hospital, 4-20-1 Nagamachiminami, Taihaku-ku, Sendai, Miyagi 982-8523, Japan. email: yogawa@kohnan-sendai.or.jp.