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.^{4,5} In addition, recent advances in coronary stenting procedures have rapidly increased the need for treatment with dual antiplatelet agents.⁵ 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.^{4,5,21,28} 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.^{1–3,6–19,21–25,29,30,32–38} How-

ever, procedures without discontinuation of antithrombotic treatment have received little attention,³⁹ and the perioperative period in neurosurgical procedures has also been less well studied.^{20,26,27,31,40–42}

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

ABBREVIATION PT-INR = prothrombin time–international normalized ratio.

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years [mean 68.2 years]) with sellar and parasellar tumors were treated via a transsphenoidal approach by a single surgeon (Y.O.), accounting for 2.51% of all transsphenoidal 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 antiplatelet agents and 4 with anticoagulant agents. The prothrombin time–international normalized ratio (PT-INR) was measured preoperatively before administering 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 antithrombotic 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 transsphenoidal 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 transsphenoidal 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 software (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 postoperative 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 preoperative tumor volume (antithrombotic agent group vs control: 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 antithrombotic 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 varied 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

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

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.

TABLE 2. Results of surgery with antithrombotic therapy

Case No.	Histology	Vol (ml)	Blood Loss (ml)	Operation Time (mins)	Removal Rate (%)
1	Atypical adenoma	1.89	130	164	100
2	Rathke's cleft cyst	0.86	230	114	100
3	Plurihormonal adenoma	1.16	125	149	100
4	Rathke's cleft cyst	0.94	485	162	100
5	Rathke's cleft cyst	0.09	100	137	100
6	Acromegaly	3.04	150	127	100
7	Plurihormonal adenoma	4.39	290	228	100
8	Rathke's cleft cyst	0.5	125	123	100
9	Gonadotroph cell adenoma	0.6	300	144	100
10	Mixed GH & PRL adenoma	5.46	460	171	100
11	Pachymeningitis		115	241	Biopsy
12	Plurihormonal adenoma	9.01	425	237	96
13	Null cell adenoma	2.89	205	131	100
14	Corticotroph cell adenoma	0.01	290	195	100
15	Chordoma	3.4	400	194	100

Discussion

The risk of thrombosis has been estimated for some systemic diseases or conditions.^{4,5,28} 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.²¹ 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.⁴ 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 ther-

apy.^{4,5,21,28} 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.¹² 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.^{20,26,27,31,42} Temporary discontinuation of antithrombotic therapy or introduction

TABLE 3. Results of surgery without antithrombotic therapy

Case No.	Age (yrs), Sex	Pathology	Vol (ml)	Blood Loss (ml)	Operation Time (mins)	Removal Rate (%)
16	28, F	Lactotroph cell adenoma	0.05	135	156	100
17	54, F	Acromegaly	4.82	245	199	98
18	58, M	Nonfunctioning	1.89	185	147	100
19	46, M	Plurihormonal adenoma	3.56	150	164	100
20	71, F	Plurihormonal adenoma	2.28	163	157	100
21	41, M	Pituitary apoplexy	2.57	134	119	100
22	65, F	Plurihormonal adenoma	0.91	353	145	100
23	66, M	Plurihormonal adenoma	3.23	345	120	100
24	56, F	Plurihormonal adenoma	0.84	180	123	100
25	62, F	Mixed GH & PRL adenoma	0.32	100	119	100
26	70, M	Plurihormonal adenoma	5.86	350	191	100
27	81, M	Plurihormonal adenoma	3.63	120	155	100
28	81, M	Somatotroph cell adenoma	11.02	535	190	95
29	55, F	Plurihormonal adenoma	6.55	135	148	100
30	32, F	Plurihormonal adenoma	0.19	100	116	100

of bridging therapy is rarely mentioned in cases of internal carotid artery dissection,⁴⁰ as is placement of cutaneous-ventricular drainage for patients after intravascular treatment.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.