The Efficacy of Ozagrel Sodium as a Rescue or Prophylaxis in the Perioperative Management of Thromboembolism during Coil Embolization of Ruptured and Unruptured Cerebral Aneurysms

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Abstract

Objectives: Thromboembolism is the leading cause of neurological complication in neurointervention. We retrospectively analyzed the incidence and the outcome of thromboembolism and the efficacy of ozagrel sodium during coiling embolization of saccular cerebral aneurysm.

Materials and Methods: Since 2012, we treated 103 patients with 106 aneurysms, in whom 116 procedures were performed. 35 patients were male, and 68 patients were female. The median age was 66.5 years (range 21 to 88). Sixty-two aneurysms were ruptured, and 44 aneurysms were unruptured. In a patient, coil embolization of a ruptured aneurysm and an unruptured aneurysm was performed simultaneously. Retreatment was performed in 12 patients. Ozagrel sodium, a thromboxane A2 synthase inhibitor, was administered as a rescue in 8 patients and as a prophylaxis in 17 patients prior to or during the procedure, and thrombectomy using Penumbra system® was performed in a patient. Functional outcome was assessed using Modified Rankin Scale (MRS).

Results: Thromboembolic events occurred in 27 procedures (23.3%), in 13 of which thromboembolism were symptomatic. Cerebral artery occlusion was observed in 9 patients during and after the procedure, in 6 of whom early recanalization could be achieved. Procedure-related permanent neurological deficit due to thromboembolism was observed in 6 patients (5.2%) exclusively in ruptured group; three of them had fair outcome of MRS 2-3 and other three patients had poor outcome unrelated to thromboembolism. None of 17 patients in whom ozagrel sodium was prophylactically administered had permanent neurological deficits due to thromboembolism. No intracranial bleeding complication was observed after administration of ozagrel sodium.

Conclusion: Ozagrel sodium can be a viable option in the perioperative management of endovascular embolization of ruptured and unruptured cerebral aneurysms.

Introduction

Although endovascular coiling has been accepted as the standard treatment of ruptured and unruptured cerebral aneurysms, thromboembolism during and after the procedure still remains the most important adverse event [1,2]. Reported incidence of thromboembolic complication varies from 8% to 28% of the cases depending on the case selection, definition and the method of detection [3-6]. However, most of thromboembolic events during the procedure can be successfully managed without clinical consequence [5], and reported incidence of procedure-related morbidity and mortality due to thromboembolism is 3% to 6.8% [4,6-9]. Ozagrel sodium is a Thromboxane A2 (TXA2) synthetase inhibitor and has been approved as an antiplatelet injection drug and in the prophylaxis of vasospasm after subarachnoid hemorrhage for clinical use in Japan [10]. Because TXA2 acts as vasoconstrictor and platelet aggregator in the ischemic brain [11], ozagrel sodium reduces hypoperfusion and cerebral edema by restricting the generation of TXA2 and facilitating the generation of prostacyclin [12]. We retrospectively analyzed the incidence and the outcome of thromboembolism and evaluated the efficacy and safety of ozagrel sodium during and after coil embolization of saccular cerebral aneurysm.

Table 1: Thromboembolic events Demographic and clinical characteristics of the patients and the treatment results are summarized.

Characteristics	Number
Gender	
Male	35 (34.0%)
Female	68 (66.0%)
Age	
<40	11 (10.7%)
40-49	6 (5.8%)
50~59	14 (13.6%)
60~69	33 (32.0%)
70~79	26 (25.2%)
>79	13 (12.6%)
Location	
ACA	32 (30.2%)
MCA	11 (10.4%)
ICA	45 (42.5%)
VBA	18 (17.0%)
Clinical presentation	
Ruptured	62 (58.5%)
Unruptured	44 (41.5%)
dome size	
>=10mm	15 (14.2%)
>=5mm, <10mm	47 (44.3%)
<5mm	44 (41.5%)
Neck size	
>=4mm	34 (32.1%)
<4mm	72 (67.9%)
Shape	
Round	55 (51.9%)
Irregular	51 (48.1%)
Technique	
Simple	64 (55.2%)
Balloon-remodeling technique	22 (19.0%)
Stent-assisted embolization	22 (19.0%)
Double catheter	17 (13.5%)
Raymond and Roy classification	
class1	49 (42.2%)
class2	39 (33.6%)
class 3	18 (15.5%)

Materials and Methods

Patients, diagnosis and treatments

Institutional review board approval was obtained for this study. Since 2012, we treated 103 patients with 106 aneurysms, in whom 116 procedures were performed at National Hospital Organization Kyoto Medical Center and Kyoto Katsura Hospital. Twelve patients with dissecting and fusiform aneurysms and two patients in whom endovascular coiling was attempted and eventually switched to surgical clipping without attempted coil deployment were excluded from the analysis. Thirty-five patients were male, and 68 patients

were female. The median age was 66.5 years (range 21 years to 88 years). Sixty-two aneurysms were ruptured, and 44 aneurysms were unruptured. In a patient, coil embolization of a ruptured aneurysm and an unruptured aneurysm was performed simultaneously. Retreatment was performed in 12 patients. For patients with SAH, CT angiography was routinely performed to determine the location of the cerebral aneurysm at admission in order to determine whether endovascular or surgical treatment should be preferable for the aneurysms. Digital subtraction angiography was routinely performed prior to the procedure for patients with unruptured cerebral aneurysms.

Endovascular procedure

Dual Antiplatelet (DAPT) drugs were routinely administered preoperatively in unruptured group, and when treated in the chronic phase, in ruptured group. Usually 100 mg of aspirin and 75 mg of clopidogrel were administered at least five days prior to the procedures. DAPT drugs were also administered preoperatively in 4 patients with ruptured aneurysms. Tube administration of 100 mg to 200 mg of cilostazol was done prior to the procedure of ruptured aneurysms in other 14 patients in ruptured group. All percutaneous procedures were performed *via* the common femoral artery with a 6 F to 8 F guide catheter. Unfractionated heparin was routinely administered intravenously after the introducer sheath placement both in ruptured group and unruptured group, with an activated clotting time of approximately 200 to 300 seconds. Double catheter technique was used in 17 patients, balloon assisted coiling was performed in 22 procedures, and stent assisted coiling was performed in 22 procedures, in 3 of which the procedure was performed in the acute phase of SAH. In 8 of 12 recurrent aneurysms, stent-assisted embolization was performed in order to achieve more packing density. In 8 patients, 40 mg to 80 mg of ozagrel sodium was initiated as a rescue treatment when cerebral artery occlusion was observed during the procedure. In one patient, thrombectomy using Penumbra system® was performed. At the end of treatment, heparin was not reversed but was discontinued. In 17 patients, ozagrel sodium was prophylactically administered prior to or during the procedure to prevent thromboembolism including 3 patients in whom stent-assisted coil embolization was performed in the acute phase of SAH.

Functional outcomes

Modified Rankin Scale (MRS) was used to assess functional outcomes 3 months after treatment or (if not available) at discharge. For the outcome analyses, modified Rankin scales were dichotomized into Rankin 0-2 (favorable outcome) and Rankin 3-6 (poor outcome). Functional outcome of MRS >2 was defined as morbidity.

Results

Thromboembolic events

Demographic and clinical characteristics of the patients and the treatment results are summarized in Table 1. Overall, 27 thromboembolic events were observed during and after the procedure, and 20 of them occurred during the procedure, 5 of them after the procedure, and in 2 of them the timing remains unknown. Fourteen of them were not related with any neurological symptoms, and 7 of them only caused transient symptoms. As a consequence, six of them were related with permanent neurological symptoms and 17 (63%) of twenty-seven patients with perioperative thromboembolisms had favorable outcomes. Four patients had hemiparesis after the procedure, and 2 had hemianopsia as a sequela:

Table 2: Summary of patients in whom ozagrel sodium was administered as a recue treatment during the procedure. M: Male; F: Female; Acom: Anterior Communicating Artery; MCA: Middle Cerebral Artery; BA: Basilar Artery; SCA: Superior Cerebellar Artery; ICA: Internal Cerebral Artery; BRC: Balloon Remodeling technique.

S.No	Age, Sex	Location, size(mm)	Neck	Presentation (SAH grade)	Adjunctive technique	Occluded vessel	Neurological sequelae	Treatment	Early recanalization	mRS
1	66, F	MCA, 4	Narrow	Ruptured (2)	Simple	MCA (M3)	Asymptomatic	Ozagrel sodium div	Yes	0
2	62, M	Acom, 13	Wide	Ruptured (5)	Simple	ACA (A2)	Hemiparesis	Ozagrel sodium div	No	5
3	72, F	BA-SCA, 6.5	Narrow	Unruptured	Simple	SCA	Asymptomatic	Ozagrel sodium(ia)	No	0
4	65, M	Acom, 5	Narrow	Ruptured (1)	Simple	ACA (A3)	Asymptomatic	Ozagrel sodium div	Yes	0
5	59, F	ICA top, 3.5	Wide	Unruptured	BRC	ACA (A2)	Transient aphasia & hemiparesis	Ozagrel (ia)+Penumbra	Yes	0
6	67, F	MCA, 3	Narrow	Ruptured (1)	Simple	MCA (M2)	Asymptomatic	Ozagrel sodium div	Yes	0
7	77, M	Acom, 4	Narrow	Ruptured (5)	Simple	ACA (A2)	Unknown	Ozagrel sodium div	No	6
8	72, M	Acom,11	Wide	Ruptured (5)	Simple	ACA (A2)	Unchanged	Ozagrel sodium div+ia	Yes	5

Table 3: Summary of 17 patients in whom ozagrel sodium was administered as a prophylaxis prior to or during the procedure. DC: Double Catheter technique; BRC: Balloon Remodeling Coiling.

S.No	Age, Sex	Location, size(mm)	Neck	Presentation (SAH grade)	Adjunctive technique	Indication	Thromboembolic events	Symptom	mRS
1	44, F	Acom, 4	Narrow	Ruptured (1)	simple	Coil protrusion	none	-	0
2	66, F	Acom,4	Narrow	Unruptured	simple	Coil protrusion	none	-	0
3	62, F	BA-SCA,5	Narrow	Unruptured	simple	thrombus	none	-	0
4	84, F	ICPC, 4	Wide	Ruptured (1)	BRC	Thrombus	none	-	2
5	59, F	Acom, 4.5	Narrow	Ruptured (3)	Simple	Coil protrusion	none	-	0
6	40, F	ICPC,	Wide	Recurrent	Stent-assisted embolization	Stent deployment	none	-	0
7	67, F	Acom, 4	Narrow	Ruptured (5)	Simple	Branch incorporation	none	-	6
8	45, F	Acom, 3	Narrow	Ruptured (1)	Simple	Coil protrusion	none	-	0
9	39, M	Acom, 3	Narrow	Ruptured (1)	Simple	Branch incorporation	none	-	0
10	71, F	ICPC, 15	Wide	Ruptured (1)	DC	Coil protrusion	MCA occlusion (recanalized)	Transient hemiparesis	2
11	83, F	BA-AICA, 3	Wide	Ruptured (1)	Stent-assisted embolization	stent deployment	none	-	2
12	78, F	VA-PICA, 5.5	Narrow	Ruptured (1)	Simple	Branch incorporation	none	-	2
13	67, F	ICPC,3.5	Short	Ruptured (1)	BRC	Thrombus	none	-	0
14	80, F	ICPC, 7	Wide	Ruptured (1)	BRC	Coil protrusion	Symptomatic infarction	Transient hemiparesis	3
15	38, F	PICA, 3	Wide	Ruptured (1)	Stent-assisted embolization	stent deployment	Asymptomatic infarction	None	1
16	68, M	ICPC, 8	Narrow	Ruptured (2)	BRC	Coil protrusion	Symptomatic infarction	Transient hemiparesis	2
17	67, F	ICPC, 7	Narrow	Ruptured (3)	DC+BRC+stent assisted embolization	Coil protrusion+stent deployment	None	-	0

the procedure-related morbidity due to thromboembolism was 5.3%. Procedure-related poor outcome rate due to thromboembolism was 1.7%. In unruptured group, 4 patients (9.3%) had thromboembolic events. Two patients had transient ischemic neurological symptoms, and two patients remained asymptomatic. One patient with ICA top aneurysm had occlusion of anterior cerebral artery at embolization of the aneurysm, and had aphasia and right hemiparesis. The occluded artery was finally reanalyzed using Penumbra aspiration catheter after immediate administration of ozagrel sodium failed recanalization of the occluded vessel, and her symptoms were completely recovered. As a consequence, perioperative procedure-related morbidity rate due to thromboembolism in unruptured group was 0%. In ruptured group, 23 patients (37.1%) had thromboembolic events. Five patients had transient neurological ischemic symptoms, 12 remained asymptomatic, and 6 had procedure-related permanent neurological deficit. Among these six patients, one patient presented with grade 5 SAH had poor outcome due to initial damage, and other two patients had poor outcome due to complication with sepsis. On

the contrary, the other three patients had fair functional outcome (MRS 2-3). Perioperative procedure-related poor outcome due to thromboembolism in this group was 3.2%. As a consequence, the presence of thromboembolic events did not affect functional outcomes both in ruptured and unruptured group. No thromboembolic events were observed in the recurrent or second-look procedure.

Efficacy of ozagrel sodium

Overall, ozagrel sodium was administered in 27 patients during or just after the procedure, 23 of whom were treated in the acute phase of SAH. In eight patients in whom cerebral artery occlusion was observed during the procedure, ozagrel sodium was immediately administered. Early recanalization was achieved in 4 patients (50%), and in another patient, complete recanalization was achieved using Penumbra aspiration catheter as shown in Table 2.
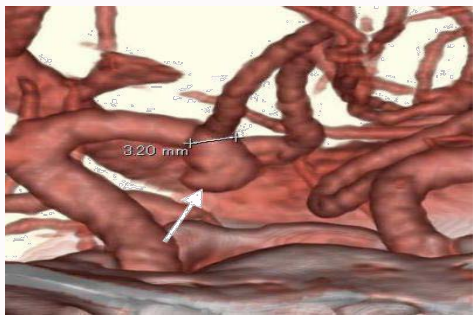
The main reasons to administer ozagrel sodium as a prophylaxis are shown in Table 4. In three patients with ruptured cerebral

Table 4: Summary of main reasons why ozagrel sodium was administered prior to or during the procedure in 27 patients.

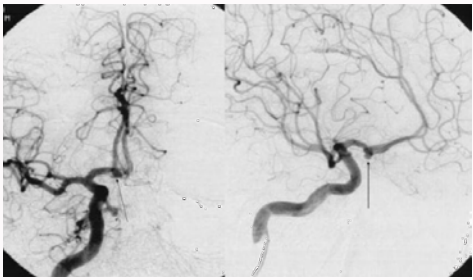| Indication of ozagrel sodium administration	
Occlusion of cerebral artery	8 (6.9%)
Symptomatic thromboembolism without large vessel occlusion	2 (1.8%)
Coil protrusion	7 (6.0%)
Stent assisted coil embolization	4 (3.4%)
Branch incorporation	3 (2.6%)
Thrombus formation	3 (2.6%)
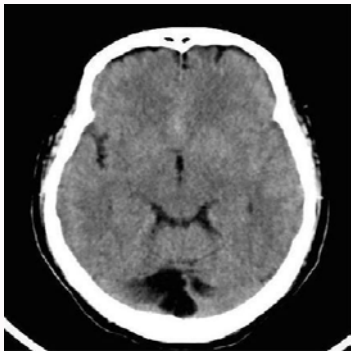
Figure 1A: Images from a 65-year old man with a ruptured aneurysm at the anterior communicating artery.
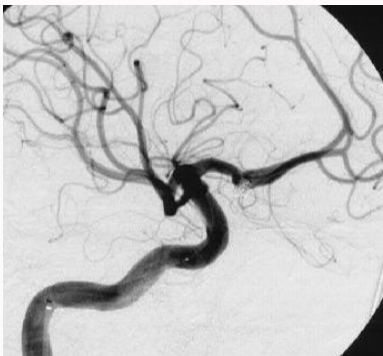

Figure 1B: Head CT shows a small amount of SAH in the anterior inter hemispheric fissure.

Figure 1C: A 3D reconstructed image also shows the small anterior communicating artery aneurysm (white arrow). The diameter of the aneurysm was 3.2 mm.

Figure 1D: The preoperative angiogram showing the anterior communicating artery aneurysm (black arrow).

Figure 1E: A postoperative angiogram shows complete occlusion of the aneurysm.
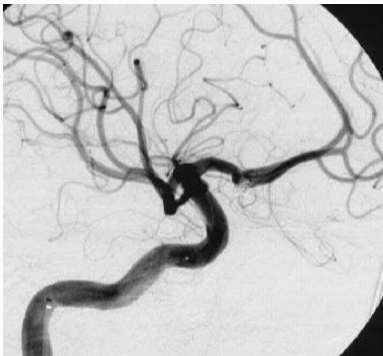
aneurysms, stent-assisted embolization was planned and ozagrel sodium was administered before the deployment of stent concurrently with 200 mg cilostazol. Although an infraction was observed in the stent-deployed territory in a patient with posterior inferior cerebellar artery aneurysm, all the stents remained patent during the follow-up period. Ozagrel sodium was also administered in 3 patients immediately after the angiographically-evident thrombus formation at the coil-to-artery junction was observed during the procedure, and they remained asymptomatic although diffusion-weighted image after the procedure showed high intensity spots in the artery territory. In three of 17 patients (17.6%) in whom ozagrel sodium was administered as a prophylaxis, transient neurological ischemic symptoms were observed after the procedure. In one patient with ruptured ICA-Pcom aneurysm in whom embolization was performed under local anesthesia using the double-catheter technique. Ozagrel sodium was administered just after the procedure because the neck of the aneurysm was very wide. She suddenly had hemiparesis during administration of ozagrel sodium, and emergent postoperative MRI showed occlusion of middle cerebral artery. Cerebral angiography was subsequently performed, and showed that recanalization

was already achieved. In one patient with ruptured aneurysm in whom embolization was performed under local anesthesia, thromboembolism was observed on the next day after the procedure. In this patient, although ozagrel sodium was administered during the procedure, addiction of anti-thrombotic agent was preserved until the effect of intraprocedural administration of heparin and ozagrel sodium was normalized and he had hemiparesis 15 hours after the procedure. His hemiparesis completely recovered after rehabilitation. In another patient with a wide-neck ruptured ICA-Pcom aneurysm, embolization was performed under general anesthesia, and she had hemiparesis the next day when she awakened from anesthesia. However, because she had a trial fibrillation and also had an infarct on the contralateral side, the timing and the source of the embolisms remained to be determined.

As a result, 5 of 9 occluded arteries during and after the procedure were recanalyzed by administration of ozagrel sodium alone, and

Figure 1F: A postoperative angiogram shows occlusion of the right anterior cerebral artery (black arrow).
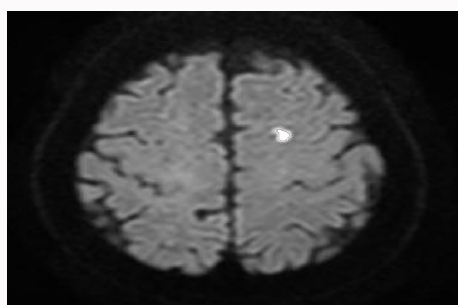
Figure 1G: The right anterior cerebral artery was partially recanalized by immediate administration of 40 mg ozagrel sodium at the end of the procedure.

6 of them were soon recanalized. Six of 9 patients who had artery occlusion during and after the procedure had favorable outcomes, and 3 other patients who were originally presented with grade 5 SAH had poor prognosis. None of 15 patients in whom ozagrel sodium was prophylactically administered had permanent neurological deficits. An enlargement of associated Intracranial Hematoma (ICH) was observed in a patient in this series, which was not observed after administration of ozagrel sodium.

Discussion

Thromboembolic events and morbidity

Thromboembolism is a leading cause of neurological complication during and after endovascular treatment of cerebral aneurysms. Although thromboembolic events can occur up to 28% of the cases, most of them can be successfully managed without clinical consequence, and reported incidence of procedure related morbidity and mortality due to thromboembolism is up to 5% [6]. The incidence rate of thromboembolic events in our series was 23.3% and procedure related morbidity was 5.2%, which was relatively high considering reported incidence. This was mainly due to high thromboembolic event rate in ruptured group. In fact, forty-five patients (72.5%) in ruptured group were treated without premedication of antiplatelet agents, and 17 of whom (37.8%) had thromboembolic events and five (11.1%) had permanent neurological deficits, which was consistent with the recent report by Edwards, et al. [13] showing 53.8% of thromboembolic event rate in the management of ruptured cerebral aneurysms without aspirin. On the other hands, although six of 18 patients who were treated with premedication had thromboembolic events, only one (5.6%) had permanent deficit. Edwards, et al. [13] also showed that thromboembolic events could be reduced to 10.6%

by administration of aspirin. Current data suggest that antiplatelet agents should be administered prior to or during the endovascular treatment of cerebral aneurysms to prevent thromboembolic events even in the acute phase of subarachnoid hemorrhage.

In our series, 9 patients (7.8%) had cerebral artery occlusions during or after the procedure, which was also in accordance with previous studies [14,15]. Brinjikji, et al. [16] demonstrated that 7% to 8% of patients who underwent endovascular treatment of intracranial aneurysms received rescue therapy using a large multihospital database.

Ozagrel sodium

There is no evidence-based guideline in the management of thromboembolic events during neurointerventional procedures. In the past, the intra-arterial thrombolysis was used, which was considered contraindicated due to catastrophic hemorrhagic complication [17,18]. Now, glycoprotein IIb/IIIa inhibitors are the most-widely used drug in the management of thromboembolic events during the procedure [14,15,19], but not available in Japan. Glycoprotein IIb/IIIa inhibitor acts as a reversible antagonist fibrinogen binding to the glycoprotein IIb/IIIa receptor of platelets and thus highly effective in inhibiting platelet aggregation [19]. Recanalization rate after use of glycoprotein IIb/IIIa a inhibitors varies from 52% to 92%, and they were reported to be less effective on distal lesions [20]. Another major concern of them is hemorrhagic complication following the procedure. One randomized control trial investigating intravenous glycoprotein IIb/IIIa inhibitor in stroke patients was stopped prematurely due to an excess of symptomatic intracranial hemorrhage [21]. A meta-analysis by Brinjikji reported that hemorrhagic complication rate after administration of glycoprotein IIb/IIIa inhibitors was 7.0% [16]. On the other hands, ozagrel sodium is a thromboxane A2 (TXA2) synthetase inhibitor and has been approved as an antiplatelet injection drug and in the prophylaxis of vasospasm after subarachnoid hemorrhage for clinical use in Japan [10,22,23]. Because complication of intracranial hemorrhage after its administration is extremely rare, it is almost routinely used in patients with acute SAH. According to the attachment, the reported incidence of intracranial hemorrhage after administration of ozagrel sodium is 1.7%. Thus, its safety is presumed to be the major advantage of ozagrel sodium. In this series, 5 (56%) of 9 patients with artery occlusion had recanalization by administration of ozagrel sodium. Recanalization of 56% seems less effective than that of glycoprotein IIb/IIIa inhibitors. Two of three patients with grade 5 SAH and two patients with unruptured cerebral aneurysms did not respond to administration of ozagrel sodium. Possible explanations were that hypercoagulability was the main cause of thromboembolisms rather than platelet aggregation in patients with grade 5 SAH, and that additional effect of ozagrel sodium as an antiplatelet drug was limited when oral antiplatelet drugs were already administered. One patient with unruptured aneurysm eventually had recanalization of occluded artery using aspiration catheter. However, considering that all 6 patients had favorable prognosis, when 3 patients who were originally presented with grade 5 SAH were excluded, ozagrel sodium can be a viable option in the management of cerebral artery occlusion during embolization of ruptured and unruptured cerebral aneurysms. In addition, ozagrel sodium was used in 15 patients as a prophylaxis in our series. It is noteworthy that no patient in this subgroup had permanent neurological deficit in spite of the fact that it was used in high risk patients for thromboembolisms.

Limitation

The limitations of the study are the retrospective nature and the small number of patients included. A third problem is the difficulty to differentiate thromboembolic events from infarcts attributable to cerebral vasospasm or cardiac emboli and determine the timing of thromboembolism. Further studies are necessary before we draw any definitive conclusions in the efficacy of ozagrel sodium. However, this is the first report ever regarding perioperative use of ozagrel sodium, and intravenous administration of ozagrel sodium has some advantage, even if off-label use, of easiness to use such as short half live, and its safety regarding the low hemorrhagic complication rate after use in patients with SAH.

Conclusion

Ozagrel sodium can be a viable option as a rescue or prophylaxis in the preoperative management of endovascular embolization of ruptured and unruptured cerebral aneurysms.

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