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Original Article

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Prasugrel versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms

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Abstract

Background: Thromboembolic complications are the main problem in stent-assisted coil embolization of unruptured intracranial aneurysms. The combination of aspirin and clopidogrel is generally used to decrease these complications, but some patients do not respond to clopidogrel and have a higher risk of stent thrombosis. In cardiology, clinical trials have shown that prasugrel reduced the incidence of ischaemic events in patients with acute coronary syndrome compared with clopidogrel but, according to several authors, prasugrel would produce an increased risk of cerebral haemorrhagic complications.

Objective: The purpose of this study was to determine whether prasugrel would be more effective than clopidogrel in reducing procedural events in patients with an unruptured aneurysm treated endovascularly with coils and stent.

Materials and methods: Two hundred consecutive patients with intracranial aneurysms were treated using coiling and stenting procedures. The first 100 patients were administered a dual antiplatelet of aspirin and clopidogrel, while the remaining 100 patients were administered a dual antiplatelet of aspirin and prasugrel. In each group data were collected on procedural and periprocedural haemorrhagic and ischaemic complications.

Results: Aneurysmal occlusion and haemorrhagic complications rates were identical in both groups. The number of thromboembolic events observed in the two groups of our study did not differ significantly, but the prasugrel group included more wide-neck aneurysms and more flow-diverted stents. Moreover, complications in the prasugrel group were more benign, explaining the significant difference in clinical outcomes between the two groups on Day 30.

Conclusions: Prasugrel reduces the clinical consequences of thromboembolic complications of endovascular treatment with stenting and coiling of unruptured intracranial aneurysms.

Keywords

Clopidogrel, coiling, intracranial aneurysm, prasugrel, stenting

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Introduction

Background/objectives

When paired with coiling, stenting procedures are able to decrease the risk of aneurysm recurrence after the endovascular treatment of intracranial aneurysms. However, this type of intervention yields higher risk rates of thromboembolic complications when compared to regular coiling procedures.[1–12]

The combination of aspirin and clopidogrel – which is generally used in these procedures – produces variable results among patients, especially given the fact that there are patients that do not respond to clopidogrel. For these groups of patients, the risk of stent thrombosis or brain ischaemia is significantly higher.[13,14]

Some authors reported a number of cases in which endovascular cerebral procedures carried out after the administration of a combination of aspirin and prasugrel yielded good clinical results, but produced an increased risk of cerebral haemorrhagic complications.[15,16]

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This prospective study was carried out with the express agreement of the hospital's ethics committee and aimed to evaluate the effectiveness and risks associated with coiling and stenting treatments in cases of non-ruptured intracranial aneurysms following the administration of aggregation inhibiting drugs – i.e. aspirin and prasugrel – in preoperative, intraoperative and postoperative conditions. The data collected for this study includes procedural and periprocedural haemorrhagic and ischaemic complications, as well as angiographic and clinical results collected both immediately after the intervention and six months following the intervention. The results were compared to those produced by a reference group which received treatment with clopidogrel and aspirin.

Patients and methods

Study design

The study draws a comparison between two consecutive groups of patients which were subjected to coiling and stenting procedures in order to treat non-ruptured aneurysms (or aneurysm recurrence). One of these patient groups was administered a dual antiplatelet of aspirin and clopidogrel, while the other was administered a dual antiplatelet of aspirin and prasugrel. This study was designed, conducted, analysed and written independently of industry or any other financial support. All human studies have been approved by the Nice Hospital ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Setting

Two hundred patients with intracranial aneurysms were treated using coiling and stenting procedures between January 2009–February 2014 at the Nice University Hospital in Nice, France. Group 1 consists of the first 100 patients treated between January 2009–January 2012, while Group 2 consists of the remaining 100 patients treated between February 2012–February 2014. The same two senior surgeons operated on all the patients in both groups.

The following data were analysed for both groups: procedural and periprocedural haemorrhagic and ischaemic complications in the six months following the intervention; postoperative angiographic results; clinical results collected one month after the intervention; clinical results collected six months after the intervention.

Participants

During the period of inclusion, all patients who were subjected to coiling and stenting of non-ruptured intracranial aneurysms or recurring aneurysms were included in the study. Patients treated surgically were excluded. Patients with ruptured aneurysms and subjected to emergency stenting were excluded from the study. Patients who received endovascular treatment (coiling, coiling with balloon) without stenting were also excluded from the study.

All patients in Group 1 received aspirin and clopidogrel – the treatment involved a daily dose of 75 mg of aspirin and 75 mg of clopidogrel, administered orally. The treatment started seven days before the endovascular intervention and continued for a period of at least six months after embolization.

Group 2 patients received a dual antiplatelet of aspirin and prasugrel. They did not receive any clopidogrel. The seventh day before treatment, a 60 mg loading dose of prasugrel was administered to the patients; then the treatment continued with a daily dose of 10 mg for a period of six months after embolization. Group 2 patients received the same dose of aspirin as the Group 1 patients.

MRI (magnetic resonance imaging) and/or CT scan (computed tomography scanner) control was carried out for patients with a clinical worsening after the procedure.

Data sources: measurement

The following parameters were analysed in both groups:

1. Clinical evaluations before and after (for a period of 1–6 months) the procedure were carried out by two senior neurovascular surgeons. They scored the results using the Modified Rankin Scale (mRS) in order to assess the degree of clinical worsening suffered by patients following the intervention.
2. Procedural thromboembolic complications: complications that were highlighted either in the angiograms during and after the embolization procedure, either during the postoperative MRI scans, carried out if there was a clinical worsening after the procedure. Angiographic findings were classified as follows: type 1: non-occlusive clot at parent vessel coil interface or in stent; type 2: occlusive clot in stent or in parent artery; type 3: distal emboli.

Both the absence or occurrence of intraoperative thromboembolic complications and the type of complications were validated by a non-interventional neuroradiologist and a neurovascular surgeon who reviewed and analysed the postoperative MRI, and the angiograms obtained during the embolization procedure.

1. Cerebral haemorrhage after endovascular treatment: complications highlighted either by the extravascular escape of the contrast fluid during the angiogram or the results of the post-embolization MRI scans and/or CT scans carried out for patients with intracranial bleeding symptoms.

Table 1. Population characteristics.

		Group 1 (clopidogrel)	Group 2 (prasugrel)	*p* Value
Patients (*n*)		100	100	
Sex (M/F)		(31/62)	(32/68)	0.87901
Age	Mean	53	54	0.7945
	Minimum	21	27	
	Maximum	73	81	
Comorbidities and history	Smokers (*n*)	47	48	0.8874
	Chronic arterial hypertension (*n*)	43	43	1
	Patients with history of aneurysm or subarachnoid haemorrhage (*n*)	36	23	0.06
	Polycystic kidney disease (*n*)	6	2	NSD
	Familial cerebral aneurysmal disease (*n*)	3	4	NSD
	History of ischaemic stroke (*n*)	4	6	NSD
	History of peripheral arterial occlusive disease and/or coronary heart disease (*n*)	4	4	NSD
mRS before the procedure	mRS 0 (*n*)	93	88	0.2279
	mRS 1 (*n*)	7	12	0.2279
	mRS 2 and more (*n*)	0	0	0

mRS: Modified Rankin Score; NSD: no significant difference.

2. Other intraoperative complications related to the procedure or occurring during the procedure (e.g. coil migration).
3. Rescue treatments for complications.
4. Post-procedure aneurysm occlusion rate was assessed using the modified Raymond Classification.[17]

Efforts to address potential sources of bias

To reduce sources of bias in the study, the preventive treatment of thromboembolic complications was the only parameter that differed between the two groups.

Statistical methods

First, descriptive statistics were estimated for each covariate within each treatment group (percentages for qualitative covariates, mean and standard deviation (SD) for quantitative ones). Second, bivariate statistical tests were provided to compare the two treatment groups: Pearson chi-square test for qualitative covariates (or Fisher exact test if necessary) and Wilcoxon non-parametric ranked test for quantitative covariates. Statistical analyses were provided by using R3.1.3 software, 2015 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants and methods

Participants. Two hundred and forty patients with non-ruptured cerebral aneurysm were initially included. Five patients treated by clipping and 35 patients treated endovascularly but without stent were excluded. Two hundred patients, treated using endovascular coil embolization, were finally included in the study.

Group 1 characteristics (Table 1, Table 2). The endovascular stents used during the procedures were Leo stents (Balt), except for two cases which used Solitaire stents (Covidien Corp.), two other cases which called for Neuroform stents (Stryker Corp.) and one aneurysm which was treated using a flow diverter (Silk, Balt).

The method used for treating the 91 aneurysms was the coiling of the aneurysmal sack assisted by balloon remodelling and a final stenting; 11 cases were treated using 'jailing' techniques.

Group 2 characteristics (Tables 1 and 2). The endovascular stents used during the procedures were: flow diverter stents (Silk Balt) in 11 procedures; Leo stents (Balt) in 81 procedures; Solitaire stents (Covidien Corp.) in nine procedures. Four procedures called for a Y-shaped stenting (using Solitaire stents).

The method used for treating the 77 aneurysms was the coiling of the aneurysmal sack assisted by balloon remodelling and a final stenting; 28 cases were treated using 'jailing' techniques.

Main results

Initial comparability of groups 1 and 2 (Tables 1 and 2). Group 1 patients (clopidogrel) showed a significantly higher number of aneurysms located in the area of the anterior communicating artery ($p = 0.01$) and more treatments for recurrent aneurysms after initial coiling ($p = 0.039$).

Table 2. Aneurysms and procedures.

		Group 1 (clopidogrel)	Group 2 (prasugrel)	*p* Value
Aneurysms/ procedures	(*n*)	102	105	
Indication	Asymptomatic aneurysm (*n*)	77	86	0.25941
	Recurrent aneurysm (*n*)	25	14	**0.03979**
	Compressive aneurysm (*n*)	0	5	0.05962
Location	ACI	35	36	0.99661
	Co Ant	32	17	**0.0102**
	MCA	25	37	0.09204
	ACA	4	4	1
	Post circ.	6	11	0.22877
Size	(>10 mm)	25	31	0.41687
Neck	(large)	61	80	**0.01143**
Postop aneurysm occlusion[a]	Score 1	73	71	0.53696
	Score 2	27	26	0.77824
	Score 3	2	8	0.10122
Flow diverter stent	(*n*)	1	11	**0.005**

ACA: anterior cerebral artery; ACI: internal carotid artery; Co Ant: anterior communicating artery; MCA: middle cerebral artery; Post circ.: posterior circulation.
[a]Raymond Scale.[17]
Bold face values for significant *p*.

Table 3. Complications.

			Thromboembolic complications		Hemorrhagic complications		
	Overall complications	Clinical worsening day 30	Overall	Stent thrombosis (type 2)	Intracranial	Extracranial	Other operative complications
Overall							
Group 1 (clopidogrel) (100 patients)	25	15	17	3	2	3	3
Group 2 (prasugrel) (100 patients)	18	6	12	0	2	4	1
p Value	0.5229	**0.0379**	0.315	$p = 0.2$	1	0.898	0.621

Bold face values for significant *p*.

Although the size of the aneurysms was constant across the two groups, the number of wide-necked aneurysms was significantly higher in Group 2 prasugrel ($p = 0.011$). Apart from these three findings, there were no statistical differences registered among the populations (as seen in Tables 1 and 2).

In terms of procedural methods, the two groups were set apart by a more frequent use of flow diverter stent in Group 2 prasugrel (11 procedures) compared to Group 1 clopidogrel (one procedure) ($p = 0.005$).

Aneurysmal occlusion (Table 2). Aneurysmal occlusion rates were identical in both groups. Group 1 had 73 completely occluded aneurysms and Group 2 had 71 ($p = 0.53$); 27 aneurysms in Group 1 and 26 aneurysms in Group 2 were classified as class 2 on the Raymond scale ($p = 0.77$). Class 3 was more frequent in Group 2 (eight in Group 2 as opposed to two in Group 1); however, this difference was not that significant ($p = 0.1$).

Total number of complications (Table 3). Group 1 presented 25 complications (20 intraoperative and five additional with 30 days) versus 18 (12 intraoperative and six postoperative) in Group 2. This was not statistically significant ($p = 0.52$) but there was a statistical significant finding in the morbidity at 30 days and six months between the groups.

No deaths were recorded across the two groups. No complications were observed in the postoperative stage across the two groups between Day 30 and the sixth month following the intervention. Six months after the

intervention, 10 patients in Group 1 showed a clinical worsening related to the intervention (seven classified as one on the mRS scale, two classified as two on the mRS scale and one classified as three on the mRS scale). However, in Group 2, only four patients had not returned to their initial clinical state (three classified as one on the mRS scale and one classified as three on the mRS scale).

Intra- and extracranial haemorrhagic complications were comparable in both groups (p = 1) (Table 3). In both groups, intra-operative bleeding was observed only for a single patient. Bleeding was not spontaneous: it resulted from mechanical perforation by the microwire with extravasation of contrast. In both, inflation of the remodelling balloon and placement of a coil stopped the haemorrhage. The Group 1 patient (clopidogrel) was hemiplegic on awakening and postoperative CT scans revealed a small-sized cerebral hematoma; the patient's condition was classified as two on the mRS scale one month after the intervention and as one on the mRS scale six months after the intervention. The Group 2 patient (prasugrel) showed a small meningeal haemorrhage, which produced headaches during the first week after the operation without any evidence of neurological disorders. In Group 2 (prasugrel) another case of intracranial bleeding (low-volume intraventricular haemorrhage) was discovered following acute headaches, one week after the intervention.

In addition to these intracranial haemorrhages, four haematomas in the groin area were observed in each group. Three weeks after the intervention, one patient in Group 2 (prasugrel) presented a gastric haemorrhage from peptic ulceration. Aspirin was stopped for three weeks and no further haemorrhage occurred.

Thromboembolic complications (Table 3). Intraoperative thromboembolic complications in the 30 days following the procedure were higher in Group 1 clopidogrel (17 patients in Group 1 versus 12 patients in Group 2), but not statistically significant ($p = 0.31$).

No thromboembolic complications were observed after Day 30, as most of the complications occurred during the intraoperative stage (16 out of 17 in Group 1; 10 out of 12 in Group 2).

In Group 2 prasugrel, thrombo-embolic complications consisted mainly of small distal emboli, which were visible on the intraoperative angiograms (three patients) or during the postoperative MRI scans (four patients), but no proximal artery occlusion and no stent thrombosis was observed. However, in the Group 1 clopidogrel, three patients showed symptomatic proximal artery thrombosis (two stent thrombosis during the intraoperative stage and one stent thrombosis occurred on Day 5).

Other intraoperative events were very similar in both groups (p = 0.621) (Table 3). The following events were observed in Group 1: an allergy to curare, which resulted in anaphylactic shock after the induction of anaesthesia; one coil rupture and one bad opening stent. In Group 2, only a coil rupture was observed.

Discussion

Compared to simple coiling procedures or balloon assisted coiling, procedures that combine stenting and coiling can reduce risks of aneurysm recurrence after an endovascular treatment.[1,12,18,19]

However, intracranial stenting, mostly indicated in the treatment of non-ruptured lesions, increases the risk of thromboembolic complications as opposed to simple coiling procedures, in spite of the dual antiplatelet.[1–12]

Thromboembolic complications vary between 7%[20] and 20%.[21,22] More serious thromboembolic complications are intrastent thrombosis which, according to McLaughlin et al.,[23] can manifest in 4.6% of cases.

The dual antiplatelet surrounding stenting procedures mostly consists of aspirin and clopidogrel.[12]

Aside from the thrombogenicity of intracranial stents, the increase in intraoperative or postoperative thromboembolic events can be explained by the inconstant effectiveness of clopidogrel, ineffective for 5–11% of patients.[13,24–26] The measurement of platelet inhibition level after clopidogrel administration is useful in quantifying the risk of thromboembolic complication in subjects undergoing endovascular treatment using implantable materials[27,28] and a significant association was observed between perioperative thromboembolic events and low-responders to clopidogrel.[24,25,27–30] The concept of a 'tailored treatment' by increasing clopidogrel dosing according to the degree of responsiveness of a given patient assessed by a platelet function assay is well known in cardiology, but for some authors[31] there is not a standardised platelet function test able to identify low-responders to clopidogrel in an easy and conclusive way; for others, the benefit of this strategy is not clear[26,32] and, finally, major bleedings are more common with double-dose than with standard-dose clopidogrel.[33]

Novel antiplatelet drugs were found to be an alternative to clopidogrel resistance; among them, prasugrel, a third generation thienopyridine, that needs hepatic biotransformation into its active metabolite to irreversibly block the P2Y12 receptor.[34]

Prasugrel has several pharmacological advantages over clopidogrel, because it is more effectively converted into its active metabolite and displays a faster onset of action and greater degree of platelet inhibition with less variability in response, even when compared with high-dose clopidogrel.[34]

Cardiology studies showed that patients who receive prasugrel exhibit major haemorrhages more frequently than patients who receive clopidogrel, especially in patients with previous strokes, elderly patients (more than 75 years) and slim patients (weight lower than 60 kg).[33,35] However, the increased risks associated with prasugrel were not found in other cardiology series,[36,37] Until now, usage of prasugrel in

cerebrovascular diseases field has been limited[16,38–42] by the fear of risk of intracranial haemorrhage. While Akbari et al.[39] described nine complications involving cerebral and extracerebral haemorrhages (out of 25 procedures), a more recent study,[42] had contradictory conclusions with a very low rate of haemorrhagic complications. This study compared the efficacy of two antiplatelet medications, low-dose prasugrel and clopidogrel, in 194 patients undergoing endovascular treatment of unruptured aneurysms and, as for our study, did not show any significant difference between the two groups in terms of intraoperative or postoperative haemorrhages. The low number of haemorrhagic complications, in the prasugrel group, compared to cardiology studies[43,44] might be due to the selection of patients subjected to treatments aimed to preventing cerebral aneurysms ruptures (good general health, age < 75 years). In terms of extracerebral haemorrhagic complications, although the number of haematomas at the puncture point was nearly consistent across the two groups involved in our study, one patient in Group 2 prasugrel exhibited an ulcerous gastric haemorrhage in the 30 days following the procedure, which called for an endoscopy and a temporary stop of prasugrel. This gastric complication was already reported in the study of Akbari et al.[39] and, as such, could imply the need for patients to be checked for gastric ulcer antecedents before being prescribed a prasugrel treatment.

In cardiology, clinical trials have shown that prasugrel reduced the incidence of ischaemic events in patients with acute coronary syndrome, compared with clopidogrel.[35,37,43,45,46] In terms of endocerebral procedures, the most important studies come to contradictory conclusions. As such, the study of Akbari et al.[39] showed no differences in thromboembolic complications in 25 patients treated with prasugrel compared with 51 patients treated with clopidogrel, and the study of Stetler et al.[38] did not report any thromboembolic complications with prasugrel. In the recent study of Ha and colleagues,[42] including the treatment of 194 patients, the authors found thromboembolic complications neither in the prasugrel group nor in the clopidogrel group. The number of thromboembolic events observed in the two groups of our study did not differ significantly. An important thing to mention in regard this finding is that the two groups were quite different in terms of operative risks: the prasugrel group had a significantly higher number of wide-necked aneurysms and was subjected to more procedures with a stent flow diverter, which is associated with higher risk of thromboembolic complications.[47,48]

Moreover, serious thromboembolic events, such as complete thrombosis of the stent, were not observed in the prasugrel group, whereas they occurred three times in the clopidogrel group. The benign character of complications that occurred in the prasugrel group accounts for the significant difference in clinical results between the two groups on Day 30.

Our study is not without limitations, including: a study population derived from both retrospective and prospective data; two consecutive populations that are different in terms of the locations in which the aneurysms have occurred, the number of wide-necked aneurysms, the use of flow diverter stents etc.; the majority of patients have undergone treatments aimed to prevent cerebral aneurysms rupture which makes it hard to generalise the results obtained in this study; the lack of systematic postoperative MRI scans.

Conclusions

The use of prasugrel instead of clopidogrel in the antiplatelet treatment accompanying the endovascular treatment of non-ruptured cerebral aneurysms can potentially decrease the clinical consequences of intraoperative and postoperative thromboembolic complications without increase of haemorrhagic events.

Declaration of conflicting interests

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