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Cerebral Aneurysm Perforations Complicating Therapy with Guglielmi Detachable Coils: A Meta-Analysis

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BACKGROUND AND PURPOSE: **The risk of intraprocedural aneurysm perforation in patients with previously ruptured aneurysms tends to be higher than that of patients with previously unruptured aneurysms, but a statistically significant difference has not been shown. Our purpose was to define the rates of occurrence and of morbidity and mortality associated with aneurysmal perforation associated with coil embolization.**

METHODS: **A meta-analysis of the results from 17 published retrospective reports of aneurysm perforations complicating therapy with Guglielmi detachable coils (GDCs) was performed. Rates of perforation and associated morbidity and mortality in previously ruptured and unruptured aneurysms were calculated. The mechanism of perforation was noted.**

RESULTS: **The risk of intraprocedural perforation was significantly higher in patients with ruptured aneurysms compared with patients with unruptured aneurysms (4.1% vs 0.5%; $P < .001$). The combined risk of permanent neurologic disability and death associated with intraprocedural aneurysm perforation was 38% for ruptured aneurysms and 29% for unruptured aneurysms. The morbidity and mortality rates with perforations caused by coils (39%) and microcatheters (33%) were similar. The morbidity and mortality rate for microguidewire perforations was considerably lower (0%, n = 4) than the rates for coils and microcatheters, but number of cases was too low to indicate statistical significance.**

CONCLUSION: **The risk of aneurysm perforation during GDC therapy is much higher in patients with previously ruptured aneurysms than in those with unruptured aneurysms. The morbidity and mortality rates are substantial for perforations caused by coils and microcatheters, whereas they seem to be much lower for perforations caused by microguidewires.**

The complication of aneurysm perforation during the therapeutic embolization of cerebral aneurysms with Guglielmi detachable coils (GDCs) has been reported in numerous retrospective studies (1–19). Some of these studies examined the overall complication rates in patients undergoing GDC therapy (1, 2, 4, 6–8, 11–13, 15, 18), whereas others specifically examined the occurrence of intraprocedural aneurysm perforation (3, 5, 9, 10, 14, 16, 19). The risk of intraprocedural aneurysm perforation in patients with previously ruptured aneurysms has tended to be higher than the risk in patients with previously unruptured aneurysms, but a statistically significant difference has not been shown. Showing such differences in the risk between various populations is difficult because the risk of intraprocedural aneurysm perforation in any population is low; therefore, data from a large patient population must be accumulated to assess the statistical significance. A clearer understanding of the factors associated with intraprocedural aneurysm perforation during GDC therapy is essential for reducing the occurrence and the associated morbidity and mortality.

Enough data to perform a statistically relevant comparison between complication rates for various patient subgroups can be accumulated by combining data from several studies through the process of meta-analysis (20). In this study, we used meta-analysis to specifically define the risk of intraprocedural aneurysm perforation in patients undergoing GDC embolization therapy.

Methods

We performed a computerized MEDLINE search of the literature from January 1990 to January 2002 for reports of GDC embolization therapy of aneurysms by using the keywords *cerebral aneurysm, ruptured, unruptured, coil, GDC,* and

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Guglielmi in different combinations. The year 1990 was chosen as the starting date because that was the year in which the GDC was introduced for clinical study. The studies that we found in the MEDLINE search were then further evaluated for inclusion in the meta-analysis. For the purposes of this meta-analysis, we defined *ruptured* and *unruptured* as the state of the aneurysm at the time the patient was referred for GDC embolization therapy. The terms *ruptured* and *unruptured* did not reflect the absence or presence of intraprocedural perforation.

Inclusion criteria for the meta-analysis of aneurysm perforation rates were the following: 1) The study investigators reported aneurysm perforations during GDC embolization therapy, 2) the report specified whether the aneurysms being treated were previously ruptured or unruptured, and 3) the report stated the overall number of previously ruptured and unruptured aneurysms treated during the period in which the perforations occurred. The inclusion criterion for the meta-analysis of morbidity and mortality associated with perforation rate was that the report needed to include clinical data regarding the outcome of the perforation. The following were excluded: 1) reports published from the initial preliminary GDC experience (eg, Guglielmi et al, 1991 [21]); 2) studies compiling experience from the multicenter GDC trial (eg, Vinuela et al, 1997 [22]), because such reports could have represented duplicate reporting of cases from the numerous centers that participated in the trial and of cases reported separately with their experience outside of the trial; and 3) reports of GDC embolization therapy of aneurysms at a specific site (eg, posterior circulation, basilar tip) or with use of a specific technique (eg, balloon remodeling), because our goal was to assess the risk of aneurysm perforation in the general population of patients treated with GDC embolization.

The reference lists of all appropriate studies found through the MEDLINE search were checked for additional appropriate studies. All studies used were retrospective.

Aneurysm Perforation Rates.— Fourteen studies fulfilling the inclusion criteria were found (1–7, 11–16, 18). Four reports describing perforations were excluded because the total number of patients treated with GDC embolization therapy was not reported (8, 9, 10, 17). The numbers of intraprocedural perforations for previously ruptured and unruptured aneurysms and the total number of procedures performed in patients with ruptured aneurysms and in those with unruptured aneurysms were tabulated. The perforation rates for patients with previously ruptured and unruptured aneurysms were compared by using the $\div^2$ test. A P value of <0.05 was considered to indicate a statistically significant difference.

Morbidity and Mortality.— Seventeen studies fulfilling this criterion were found (1–10, 12–18). When available, data regarding the cause of the perforation (eg, coil, microcatheter, microguidewire) and the intraprocedural use of heparin was recorded. The rates of death and disability resulting from aneurysm perforation were determined. Rates of death and disability caused by perforations due to coils, microcatheters, and microguidewires were compared by using the Fisher exact test. A P value of <0.05 was considered to indicate a statistically significant difference.

Results

The data regarding rates of perforation during embolization therapy of ruptured and unruptured aneurysms are summarized in the Table. A total of 55 perforations were reported in studies that also provided the total number of GDC cases; these data allowed calculation of the perforation rates. The total number of cases of GDC embolization therapy from the reports was 2008, with 1248 ruptured aneurysms and 760 unruptured aneurysms. The risk of intraprocedural perforation was significantly higher in patients with ruptured aneurysms than in patients with unruptured aneurysms (4.1% vs 0.7%; $P < .001$).

TABLE 1: Occurrence of aneurysm perforation during therapeutic embolization with GDCs

Study*	No. of Cases	No. of Perforations†
Ruptured aneurysms		
Doerfler et al (5)	164	5 (3)
Ricolfi et al (14)	91	4 (4)
Coumans et al (3)	45	4 (10)
Cognard et al (2)	150	6 (4)
Raymond et al (13)	75	6 (8)
Vanninen et al (18)	109	3 (3)
Kuether et al (7)	32	2 (6)
Debrun et al (4)	48	1 (2)
Byrne et al (1)	75	3 (3)
Houdart (6)	218	4 (2)
Sluzewski et al (16)	182	7 (4)
Qureshi et al (12)	59	6 (10)
Total	1248	51 (4.1)
Unruptured aneurysms		
Coumans et al (3)	83	0 (0)
Cognard et al (2)	58	0 (0)
Debrun et al (4)	83	0 (0)
Kuether et al (7)	45	0 (0)
Murayama et al (11)	120	1 (0)
Sluzewski et al (16)	82	0 (0)
Houdart (6)	72	0 (0)
Roy et al (15)	125	3 (2)
Qureshi et al (12)	92	1 (1)
Total	760	5 (0.7)

* Data in parentheses are reference citations.

† Data in parentheses are percentages.

Outcome data were available in 72 cases of perforation in the reports, including 66 cases of ruptured aneurysms and six cases of unruptured aneurysms. For ruptured aneurysms, intraprocedural aneurysm perforation was associated with a 33% risk of death (22 of 66 patients) and a 5% risk of disability (three of 66 patients). For unruptured aneurysms, a 14% risk of death (one of seven patients) and a 14% risk of disability (one of seven patients) were noted.

Information about both the outcome and the mechanism of perforation was available in 65 patients. The morbidity and mortality rates with perforations caused by the coil (21 [39%] of 54 patients) and rates for those caused by the microcatheter (three [33%] of nine patients) were similar. The morbidity and mortality rates for microguidewire perforations were lower (zero [0%] of four patients) than the rates for coils and microcatheters, but this difference was not statistically significant ($P = .16$).

Information about both the outcome and the use of heparin during the procedure was available in 43 patients. The morbidity and mortality rate in patients who had not been treated with heparin was 20% (one of five). The morbidity and mortality rate in patients who were treated with heparin at the time of aneurysm perforation was 32% (12 of 38). The morbidity and mortality rates were not significantly different between patients who were treated with intraprocedural heparin and those who were not ($P = .37$).

Discussion

In this meta-analysis, we determined that the risk of intraprocedural rupture during GDC embolization therapy in patients with previously unruptured aneurysms (0.7%) was significantly lower than that of patients with previously ruptured aneurysms (4.1%) ($P < .001$). While accurately accounting for limitations such as publication bias remains impossible, we believe that these results accurately reflect the risk of perforation in GDC embolization therapy. Vinuela et al (22) reported 11 (2.7%) perforations in 403 cases of ruptured aneurysms from a multicenter trial that included some of the centers in this meta-analysis. Interestingly, data from that multicenter trial reflect early experience with the device, but they demonstrate a lower perforation rate compared with that of the current meta-analysis. Thus, the perforation rate does not seem to be decreasing as experience is gained. A trend toward embolization of smaller aneurysms since the time of the multicenter trial might explain the increased risk of perforation. The reports included in the meta-analysis are from medical centers that are quite experienced; therefore, the perforation rate with less experienced operators could be higher.

Multiple factors may be correlated with the risk of perforation with GDC embolization therapy. Intraprocedural perforation rate may reflect aneurysm size (ie, smaller aneurysms may be more likely to become perforated) and operator experience. Theoretically, smaller aneurysm size are associated with a higher risk of aneurysm rupture because random or accidental displacements of endovascular devices by a few millimeters that are trivial in a large aneurysm might lead to catastrophic rupture in the more confined lumen of a small aneurysm. Tortuosity of the arteries might increase the risk of perforation by decreasing the level of control that the operator has over the endovascular devices.

Data in the reports of perforation in the literature are incomplete regarding aneurysm location and size. Even if the location and size of the aneurysms that became perforated were well-described in all cases included in this meta-analysis, the location and size of all of the aneurysms that did not become perforated also must be known to evaluate for differences in risk that are dependant on the specific location and size. We see no theoretical reason why the location of an aneurysm might predispose it to rupture, other than that certain locations may be associated with more tortuous anatomy that could increase the technical difficulty.

The intraprocedural perforation of a previously unruptured aneurysm necessitates the de novo creation of a rent in the aneurysm wall. Intraprocedural perforation in previously ruptured aneurysms does not have this same requirement and could occur because of the dislodgement of a clot that occludes the site of original rupture or because of the additional tearing of an already torn and fragile aneurysm wall. Aneurysms with a rupture may also have a wall that is more fragile than those without a rupture. These differences probably explain the higher rate of perforation in ruptured aneurysms compared with the rate in unruptured aneurysms.

All endovascular devices placed into an aneurysm lumen can cause perforation. On the basis of our meta-analysis results, microguidewire perforations do not seem to be as life-threatening as catheter and coil perforations, although the low number of microguidewire perforations reported does not allow for adequate statistical comparison. We suspect that wire perforations are under-reported, because many operators may not take note of a minor wire perforation that does not cause contrast extravasation. Coil and catheter perforations accounted for all of the death and neurologic disabilities reported. The rate of death and neurologic disability related to each device is correlated with the size of hole that is made with each device. The size of the perforation can be expected to be correlated with the size of the device. Microguidewires commonly used to treat aneurysms have a diameter of approximately 0.33 mm (0.010–0.014 in). Microcatheters typically used for aneurysm therapy have a diameter of 0.5–1.0 mm. GDCs have a primary wind diameter similar to that of a microguidewire, but the circular memory of their secondary wind is set to a diameter of 2–20 mm. The leading end of a GDC might cause a perforation similar to that caused by a microguidewire, but loops with the diameter of the secondary wind of the GDC can cause a much larger rent in an aneurysm and probably accounts for the morbidity and mortality associated with perforations caused by the coil.

Death and permanent neurologic disability occurring as a result of intraprocedural aneurysm perforation may be somewhat dependent on patient care immediately after the perforation. Immediate reversal of heparin anticoagulation with protamine sulfate is probably wise. Anticoagulation might theoretically lead to a worse outcome with aneurysm perforation, but we did not find a statistically significant increase in morbidity and mortality rates in cases in which perforation occurred while the patient was receiving heparin anticoagulation. If a ventriculostomy is not yet present, its placement should be strongly and immediately considered. The perforating device should probably not be pulled out, because the device may be partially occluding the perforation, and pulling out the device may result in further injury to the aneurysm wall. The procedure can often be accomplished by avoiding further manipulation of the initial microcatheter and coil system and by placing a second microcatheter in the aneurysm to complete the embolization (19).

We observed slightly less morbidity and mortality with perforations of unruptured aneurysms. Because of the small number of perforations of unruptured aneurysms, statistical comparison is not practical. One might expect that patients with previously unruptured aneurysms fare worse with perforation because they will not have a ventriculostomy. Alternatively, patients with a previously ruptured aneurysm

might fare worse with perforation because repeat hemorrhage in a patient with a ruptured aneurysm is associated with an 80% mortality rate (23).

Because this study is a meta-analysis and because all of our data were obtained from multiple published reports, further evaluation of the data for important risk factors such as patient age, length of procedure, and aneurysm location was not possible. We were also unable to determine which subgroups of patients, such as the elderly, have a worse outcome with perforation. We noted heterogeneity in the way outcomes were reported. Methods of reporting outcome varied among the reports and included methods such as the Rankin Scale, the Glasgow Outcome Scale, and simple reporting of outcome descriptors such as "good," "poor," and "death." Some minor morbidity was possibly missed because the authors of a report may have described some patients with minor morbidity as having a good outcome. Heterogeneity may have existed between the studies with regard to the reporting of complications that could have led to the under-reporting of perforations, especially those that went unnoticed because the patients did not have poor outcomes. Some patients probably had neurologic deficits secondary to the initial rupture of their aneurysm and subsequent vasospasm, and the effect of an additional insult such as an intraprocedural aneurysm perforation on the outcome in such patients is not always clear.

Conclusion

The meta-analysis shows that the risk of aneurysm perforation during GDC embolization therapy is much higher in patients with previously ruptured aneurysms than in those with unruptured aneurysms. The risk of death and neurologic disability appears to be highest with perforations caused by coils and microcatheters. Continued research and experience may yield insights into how to reduce the overall rate of intraprocedural perforation and how to decrease the associated morbidity and mortality.

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