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Potential Perioperative Complications Due To Difference In Timing Of Systemic Heparinization During Ruptured Aneurysm Coiling

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Object. Systemic heparinization perioperatively is standard during ruptured aneurysm coiling. However, current guidelines do not address whether different timing protocols affects perioperative complications. This study evaluates ruptured aneurysms treated with coiling and whether differences in perioperative complication rates exist with two different treatment protocols.

Methods. 242 patients were retrospectively identified and divided based on timing of systemic heparin distribution intraoperatively. Demographic data and clinical data were collected and compared. Perioperative complications in both treatment arms were analyzed and risk of re-rupture and stroke compared.

Results. 93 patients were treated with systemic heparinization at beginning of the procedure (Protocol 1) and 149 patients were treated with systemic heparinization at the beginning and after deployment of the first coil (Protocol 2). 8 (3.31%) total patients, with 1 (1.08%) patient in Protocol 1 and 7 (4.70%) patients in Protocol 2 had perioperative re-rupture events. 6 (2.48%) of total patients, with 2 (2.15%) patients in Protocol 1 and 4 (2.68%) patients in Protocol 2 experienced perioperative stroke event.

Conclusions. Difference in timing of systemic heparinization did not appear to increase the frequency of perioperative complications.

Introduction:

Endovascular embolization of cerebral aneurysms has been widely associated with both low morbidity and mortality rates, whether ruptured or unruptured. Like many endovascular procedures, embolization is associated with a risk of perioperative thromboembolic, ischemic, as well as rebleeding complications, and these complications remain the most significant factors of poor outcomes.

Several studies have been done ascertaining other interventions that reduce thromboembolism risk without increasing hemorrhagic complications. Other studies have focused on assessing incidence of perioperative complications due to factors such as type of aneurysm treatment modality, clinical characteristics and risk factors of patients, preoperative prevention and postoperative events.

Current guidelines recommend perioperative systemic administration of heparin to reduce intraprocedural thromboembolism risk and standard dosing recommendations exist. However, there is a wide variation in protocols regarding timing of distribution during embolization procedures. Thus far, a comparative analysis has not been performed to determine differences in timing of distribution of systemic heparinization perioperatively and its effect on ischemic and hemorrhagic complication rates.

We performed this analysis to evaluate the differences, if any, on the frequency of perioperative complications in relation to the timing of intraprocedural distribution of systemic

heparin, particularly looking at if earlier administration increases bleeding diathesis and if later administration increases ischemic events.

Materials and Methods:

We retrospectively identified and reviewed prospectively collected medical records of all patients with a primary diagnosis of subarachnoid hemorrhage due to ruptured aneurysm who were treated with detachable coils at a high-volume, single center endovascular site from July 2012 to September 2020.

Patients were brought into the angiography suite and placed in supine position. Arteries are accessed with 19-gauge needle which is exchanged with a 5-8 French Terumo sheath over a wire. Under fluoroscopic guidance, 088 Neuron MAX or Balt Ballast guide catheters are advanced. Pressured saline bags are connected to guide catheters and sheath at 2000 U/L. Once parent artery is selected, Scepter XC 4x11 balloon microcatheter is advanced over a 042 Synchro-2 microwire to selectively catheterize the artery. Then a Headway 17 or sL10 microcatheter is advanced over the Synchro-2 microwire to selectively catheterize the aneurysm using Hydrogel coils. During the procedure, patients were either treated with a single dose of 35 U/kg systemic heparin at beginning of the procedure or dosing of 35 U/kg at beginning of procedure and another 35 U/kg after deployment of first coil.

Selection criteria for endovascular treatment were based on imaging and clinical criteria. Baseline demographic data included age and sex. Baseline clinical data included Hunt and Hess Scale (H/H), Modified Fisher Grade (MFg), and aneurysm size (length and neck width). Clinical outcomes included intraoperative complication rates, specifically re-rupture and stroke.

Statistical Analysis:

Overall, 242 patients were identified meeting the inclusion criteria and were subdivided into 2 groups based on the timing of distribution of systemic heparin intraoperatively, Protocol 1 and 2. Protocol 1 consisted of patients receiving 35 U/kg of systemic heparin at the beginning of the procedure (n=93) while Protocol 2 consisted of patients receiving 35 U/kg at the beginning of procedure and after deployment of the first coil (n=149).

All data were descriptively presented using mean $\pm$ standard error (SE) for continuous data and frequencies for categorical data. Comparison between continuous data was assessed using one-way ANOVA and chi-square test or Fisher's Exact Test for categorical variables. A p-value of <0.05 was considered to be significant. All statistical analyses were performed using R software package.

Results:

Of the 242 patients who underwent coil embolization of ruptured aneurysms, 93 (38.4%) treated under Protocol 1 and 149 (61.6%) treated under Protocol 2. Mean age ($\pm$ SE) of all patients was 57.66 $\pm$ 1.01 with no statistical difference between protocol arms (p-value = 0.78), 72.31% (n=175) women. Total complication rate was 5.79% (n=14), with 3.31% (n=8) having intraprocedural re-rupture of aneurysm and 2.48% (n=6) having intraprocedural ischemic event. Demographic characteristics of the patient population studied according to protocol strata can be seen in Table 1.

Univariate analysis of predictive variables and risk factors measured—Hunt and Hess Scale, Modified Fisher Grade, and aneurysm size—are shown in Table 1. Median Hunt and Hess Scale was 2 overall, 3 for Protocol 1, and 2 for Protocol 2. Frequency of patients with baseline Hunt and Hess Scale of 1 was greater in Protocol 1 than Protocol 2 (n=29 and n=18, respectively, p=0.00039) and baseline Hunt and Hess Scale of 2 was greater in Protocol 2 than Protocol 1 (n=68 and n=15, respectively, p=0.000002). Hunt and Hess Scales 3, 4, and 5 showed no significant difference between protocol strata (p=0.54, p=0.08, p=0.32, respectively). Median Modified Fisher Grade was 3 overall, 4 for Protocol 1, and 3 for Protocol 2. With respect to Modified Fisher Grade, both protocols showed no significant difference at grades 1 and 2 (p=0.16, p=0.22, respectively). However, there was a significant difference in patients graded at 3 and 4, with Protocol 2 showing a greater degree of patients graded at 3 than Protocol 1 (n=101 vs. n=37, p=0.00003, respectively) and Protocol 1 showing a greater degree than Protocol 2 graded at 4 (n=48, n=35, p=0.00001, respectively). The mean ± SE differences of aneurysm length for Protocol 1 vs. 2 (6.17 ± 0.38 vs. 6.20 ± 0.26, respectively) and width (4.78 ± 0.33 vs. 4.68 ± 0.20) did not show any significant differences (p=0.93, p=0.80).

Frequency of intraoperative re-rupture of aneurysm was recorded to be 1.08% (n=1) for Protocol 1 and 4.70% (n=7) for Protocol 2 (p=0.18) and frequency of intraoperative stroke was recorded to be 2.15% (n=2) for Protocol 1 and 2.68% (n=4) for Protocol 2 (p=1.00), failing to show any significant different between protocols for either of the endpoints.

Table 1: *Characteristics of patients and comparison of perioperative complications within Protocol cohorts*

	All Patients n= 242	35 U/kg At Start n= 93	35 U/kg At Start and After First Coil n= 149	P-Value
Age (mean ± SE)				
	57.66 ± 1.01	57.30 ± 1.70	57.89 ± 1.25	0.78
Sex				
Male (%)	67 (27.69)	28 (30.11)	39 (26.17)	0.56
Female (%)	175 (72.31)	65 (69.89)	110 (73.83)	
Hunt and Hess				
1 (%)	47 (19.42)	29 (31.18)	18 (12.08)	0.00039
2 (%)	83 (34.30)	15 (16.13)	68 (45.64)	0.000002
3 (%)	59 (24.38)	25 (26.88)	34 (22.82)	0.54
4 (%)	43 (17.77)	22 (23.66)	21 (14.09)	0.08
5 (%)	10 (4.13)	2 (2.15)	8 (5.37)	0.32
Median	2	3	2	
Modified Fisher Grade				
1 (%)	9 (3.72)	1 (1.08)	8 (5.37)	0.16

2 (%)	12 (4.96)	7 (7.53)	5 (3.36)	0.22
3 (%)	138 (57.02)	37 (39.78)	101 (67.79)	0.00003
4 (%)	83 (34.30)	48 (51.61)	35 (23.49)	0.00001
Median	3	4	3	
Aneurysm Size (mean ± SEM)				
Length (mm)	6.19 ± 0.22	6.17 ± 0.38	6.20 ± 0.26	0.93
Width (mm)	4.73 ± 0.18	4.78 ± 0.33	4.68 ± 0.20	0.8
Perioperative Complications (%)				
Re-rupture (%)	8 (3.31)	1 (1.08)	7 (4.70)	0.18
Stroke (%)	6 (2.48)	2 (2.15)	4 (2.68)	1.00

Discussion:

Systemic distribution of heparin during endovascular procedures has been shown to decrease the incidence of intraoperative complications, however standard guidelines as to timing of this distribution and its effect on intraoperative complications has not been studied thus far. The goal for this study was to compare whether differences in timing of distribution of systemic heparin during ruptured aneurysm coiling would cause differences in intraoperative rebleeding and ischemic events, specifically whether patients receiving earlier heparinization were at increased risk for aneurysm rebleeding and whether later distribution would increase ischemic events. This study has shown that patients undergoing systemic heparinization at the start of procedure vs. after first coil has been dispensed when treating ruptured intracranial aneurysm has no difference in effect on perioperative complication rate, whether it be bleeding or ischemic events.

Despite some significant difference between predictive factors, particularly Hunt and Hess scoring and Modified Fisher Grade, and similar baseline demographics, the outcome in perioperative complication rates do not vary significantly between protocol arms and are in line with rates found in other studies. Ries *et al*, performing a study comparing intraprocedural distribution of system heparin vs heparin + acetylsalicylic acid, found that complication rates for thromboembolic events ranged from 2.4%-5.2% while frequency for aneurysm rebleeding ranged from 2.3%-4.3% (n=261). Similarly, a meta-analysis by the Ontario Medical Advisory Secretariat found aneurysm coiling was associated with intraoperative thromboembolic events ranging from 2.5%-14.5% and re-rupture rates ranging from 2.3%-4.7%. Pierot *et al*, in a multicenter study of intraoperative complication rates when comparing coiling and balloon-assisted coiling, thromboembolic rate of 10.4% and re-rupture rate of 3.1% were observed (N=1088).

For the past two decades, significant research has been undertaken towards improving complication rates of ruptured aneurysm treatment. These studies have looked at different treatment modalities, preprocedural, intraprocedural, and postprocedural interventions, as well as clinical and demographic factors to assess risk. However, standard of care for intraoperative anticoagulation with systemic heparin has remained the same. Factors associated with intraoperative coagulation parameters involving systemic heparinization remain an unaddressed area of study, potentially impeding efforts at understanding the full scope of intraoperative factors contributing to complication rates. Furthermore, the wide variability in protocols among

facilities and between physicians at these facilities necessitates the assessment these parameters in order to potentially standardize treatment protocols to reduce intraoperative complication rates and, thus, reduce morbidity and mortality among patients.

Limitations:

The most important limitation in this study is its retrospective nature and single center study. This diminishes the ability to establish subgroups among patients and assess for endpoints such as preoperative risk factors that might contribute to intraoperative complications. This also contributes to the ubiquity of our finding due to the limited assessment of different timing of distribution protocols and their effect on complication rate. Further studies are indicated to increase power to better detect subgroup differences and assessing the ubiquity of these results. Large multicenter prospective studies would be necessary to corroborate these results.

Conclusion:

Our study suggests that timing of distribution of systemic heparin intraoperatively during coiling of ruptured aneurysm has no significant event on complication rates, specifically rebleeding and thromboembolic events. This area remains relatively understudied and warrants further research to establish whether timing of distribution could warrant reassessment of guidelines in periprocedural systemic heparin protocols.

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