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ORIGINAL ARTICLE

Iatrogenic arterial vasospasm during mechanical thrombectomy requiring treatment with intra-arterial nimodipine might be associated with worse outcomes

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Abstract

Background and Purpose: Vasospasm is a common iatrogenic event during mechanical thrombectomy (MT). In such circumstances, intra-arterial nimodipine administration is occasionally considered. However, its use in the treatment of iatrogenic vasospasm during MT has been poorly studied. We investigated the impact of iatrogenic vasospasm treated with intra-arterial nimodipine on outcomes after MT for large vessel occlusion stroke.

Methods: We conducted a retrospective analysis of the multicenter observational registry Endovascular Treatment in Ischemic Stroke (ETIS). Consecutive patients treated with MT between January 2015 and December 2022 were included. Patients treated with medical treatment alone, without MT, were excluded. We also excluded patients who received another in situ vasodilator molecule during the procedure. Outcomes were compared according to the occurrence of cervical and/or intracranial arterial vasospasm requiring intraoperative use of in situ nimodipine based on operator's decision, using a propensity score approach. The primary outcome was a modified Rankin Scale (mRS) score of 0–2 at 90 days. Secondary outcomes included excellent outcome (mRS score 0–1), final recanalization, mortality, intracranial hemorrhage and procedural complications. Secondary analyses were performed according to the vasospasm location (intracranial or cervical).

Results: Among 13,678 patients in the registry during the study period, 434 received intra-arterial nimodipine for the treatment of MT-related vasospasm. In the main analysis, comparable odds of favorable outcome were observed, whereas excellent outcome was

Please see Appendix S1 for ETIS investigators.

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significantly less frequent in the group with vasospasm requiring nimodipine (adjusted odds ratio [aOR] 0.78, 95% confidence interval [CI] 0.63–0.97). Perfect recanalization, defined as a final modified Thrombolysis In Cerebral Infarction score of 3 (aOR 0.63, 95% CI 0.42–0.93), was also rarer in the vasospasm group. Intracranial vasospasm treated with nimodipine was significantly associated with worse clinical outcome (aOR 0.64, 95% CI 0.45–0.92), in contrast to the cervical location (aOR 1.37, 95% CI 0.54–3.08).

Conclusion: Arterial vasospasm occurring during the MT procedure and requiring intra-arterial nimodipine administration was associated with worse outcomes, especially in case of intracranial vasospasm. Although this study cannot formally differentiate whether the negative consequences were due to the vasospasm itself, or nimodipine administration or both, there might be an important signal toward a substantial clinical impact of iatrogenic vasospasm during MT.

KEYWORDS
mechanical thrombectomy, nimodipine, vasospasm

INTRODUCTION

Mechanical thrombectomy (MT) is the first-line treatment for large vessel occlusion stroke (LVOS) [1, 2]. However, endovascular treatment can trigger arterial vasospasm during the procedure, generally related to MT maneuvers and device passes. If deemed severe, and in the absence of standardized guidelines, arterial vasospasm is occasionally treated with intra-arterial vasodilation. In situ nimodipine infusion, a relatively common and established treatment in the setting of intracranial vasospasm related to aneurysmal subarachnoid hemorrhage, is generally considered in most of these cases [3–5].

In the literature, arterial vasospasm is reported to occur in 3%–20% of MT cases [6–10]. The impact of vasospasm and the effect of its specific treatments on patient outcomes in these cases is not known [11]. The clinical impact of iatrogenic arterial vasospasm remains debated [10–12], and this event is generally not even reported among procedural complications [13]. To date, there are few available studies evaluating the influence of iatrogenic cerebrovascular vasospasm on functional outcomes and the efficacy and safety of intra-arterial nimodipine use during the acute phase of ischemic stroke [14, 15].

Our aim was to investigate the influence of iatrogenic arterial vasospasm secondary to MT and treated with intra-arterial nimodipine on the outcome of patients who received endovascular treatment for LVOS.

METHODS

Study design and population

We conducted a retrospective analysis of the multicenter prospective observational ongoing Endovascular Treatment in Ischemic Stroke (ETIS) registry [16, 17]. Local ethics committees approved data collection and analysis. Consecutive patients treated with MT between January 2012 and December 2022 were included. We excluded patients not treated with MT. We also excluded patients who received other in situ vasodilator treatments during the endovascular procedure (milrinone, isosorbide dinitrate or nicardipine). Only the intra-arterial in situ administration of nimodipine for the treatment of intracranial and/or cervical arterial vasospasm was considered in this study. Patients who received nimodipine within the saline infusions used for catheter flushing during the MT procedures—as observed in some local protocols—were not considered as having received intra-arterial nimodipine for the treatment of a targeted vasospasm because the dose administered in these cases was not precisely measurable and was considered very low.

Treatment

Intravenous thrombolysis indication and MT were based on standard guidelines [18, 19]. The anesthetic regimen relied on patient status and local protocols. The type of guiding catheter and endovascular approach (use of stent retriever alone, contact aspiration or combined approach) was chosen on a case-by-case basis according to the occlusion site and operator's habits. In the absence of standardized guidelines, the indication for the intra-arterial administration of nimodipine and the dose were decided on by operators according to the severity of arterial vasospasm assessed on the narrowing of the arterial lumen on digital subtraction angiography and/or its downstream hemodynamic consequence. Nimodipine bolus was administered in situ through the guiding catheter or the aspiration catheter.

Collected data and outcomes

Baseline patient, imaging and timeframe data, along with therapeutic and procedural characteristics, were collected. Senior

neuroradiologists locally assessed angiographic and imaging data. Three-month modified Rankin Scale (mRS) scores were collected by certified investigators during routinely scheduled visits or by trained research nurses during a standardized telephone interview. Baseline, angiographic and 24-h imaging data were locally assessed by trained (>10 years' experience) neuroradiologists or neurologists. The indication for intra-arterial nimodipine infusion was recorded as intracranial and/or cervical vasospasm. Angiographic efficacy of nimodipine was also recorded: an angiographic response was defined as a remaining stenosis of the target artery of less than 50%.

The primary outcome was favorable outcome, defined by an mRS score of 0–2 or equal to pre-stroke mRS score at 3 months. Excellent outcome was defined by a 3-month mRS score of 0 or 1. Early neurological evolution was evaluated through change in National Institutes of Health Stroke Scale (NIHSS) score between admission and Day 1. Intracranial hemorrhage (ICH) was evaluated based on imaging on Day 1 according to the European Cooperative Acute Stroke Study (ECASS-II) classification. Any ICH was defined by the occurrence of ICH of any type detected on systematic 24-h imaging, either symptomatic or not. Symptomatic ICH (sICH) was defined as any ICH on the 24-h imaging associated with an increase of 4 points or more on the NIHSS within 24 h attributable to the ICH. Parenchymal hematoma (PH) occurrence was also investigated. Variation of NIHSS score between admission and 24-h assessment, as well as change in Alberta Stroke Program Early Computed Tomography Score (ASPECTS) between initial imaging and Day 1, were collected. Procedural outcomes were successful recanalization (defined by final modified Thrombolysis In Cerebral Infarction [mTICI] score 2b, 2c or 3), excellent recanalization (final mTICI score 2c–3), perfect recanalization (defined as final mTICI score 3) and procedural complications (embolus in a new territory, perforation or other).

Statistical analysis

Quantitative variables are expressed as means (standard deviation [SD]) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distribution was assessed using histograms and the Shapiro–Wilk test. Patients were divided into two groups according to use of in situ nimodipine during the endovascular procedure for the treatment of arterial vasospasm.

Patient characteristics are described according to study group and the magnitude of the between-group differences was assessed by calculating the absolute standardized differences (ASD). An ASD >10% was interpreted as a meaningful difference.

We estimated the effect size of vasospasm treated with intra-arterial nimodipine on main angiographic and clinical outcomes before and after taking into account the potential confounding factors using propensity score (PS). The PS was estimated using a non-parsimonious multivariable logistic regression model, with study group as the dependent variable and the following covariates: age, tobacco use, diabetes, baseline NIHSS score, baseline ASPECTS, delay between symptoms onset to puncture admission mode, unknown onset time, history of hypertension, pre-stroke antithrombotic treatment, pre-stroke mRS score, location of intracranial occlusion and use of intravenous thrombolysis.

Firstly, the PS was used to weight subjects using the PS overlap weighting (PSOW) method and secondly to constitute a well-balanced group (PS-matched cohort) [20]. For the PS-matched cohort, patients from the vasospasm group were matched 1:3 to patients from the non-vasospasm group according to logit of PS using the greedy nearest neighbor matching algorithm, with a caliper width of 0.2 SD of logit of PS. To evaluate bias reduction using the PS matching method, ASDs were calculated in the PS-matched cohort.

Because of missing data on baseline characteristics and outcomes, we estimated the effect size of vasospasm treated with nimodipine in the PSOW and PS-matched adjusted analyses after handling missing covariate values by multiple imputation using a regression switching approach (chained equations with $m = 10$). An imputation procedure was performed under the missing at random assumption using all variables listed in Table 1 and all outcomes, with a predictive mean matching method for quantitative variables and multinomial or binary logistic regression models for categorical variables. In each imputed dataset, PSs were calculated to provide PSOW-adjusted effect sizes. We combined these adjusted effect sizes from each imputed dataset using Rubin's rules.

The PSOW-adjusted effect sizes of vasospasm treated with nimodipine were estimated using weighted logistic regression models for binary outcomes, weighted linear regression models for quantitative outcomes, and a weighted binomial negative model for total number of passes. In the PS-matched cohort, comparisons were made using mixed logistic regression models (binomial distribution, logit function) for binary outcomes, mixed linear regression models for quantitative outcomes and negative binomial model for total number of passes with the matched blocks as random effect.

Using group without vasospasm as the reference, we derived from these regression models odds ratio (ORs) or mean differences as treatment effect size measures, with their 95% confidence intervals (CIs). Our first analyses covered the whole study group. Sensitivity analyses restricted to patients with intracranial vasospasm and to patients with cervical vasospasm were performed using the same methodology as that described for the whole study group (only PSOW method). Patients with concurrent intracranial and cervical vasospasm were included in the intracranial vasospasm subpopulation but not in the cervical vasospasm subgroup. Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using SAS software version 9·4 (SAS Institute, Cary, NC, USA).

RESULTS

From January 2015 to December 2022, 13,678 patients were consecutively enrolled in the ETIS registry. Among them, 434 patients

TABLE 1 Patient characteristics according to the occurrence of vasospasm requiring treatment with nimodipine.

Characteristic	Vasospasm treated with nimodipine		ASD, %
	No ($n = 13,244$)	Yes ($n = 434$)	
Age, years, mean (SD)[a]	70.5 ± 14.9	62.3 ± 15.4	54.0
Men, *n* (%)	6843 (51.7)	224 (51.6)	0.2
Mothership admission[a]	5258 (39.7)	175 (40.3)	6.2
Unknown time of onset[a]	4394 (33.2)	166 (38.2)	10.5
History of hypertension[a]	8012 (60.5)	220 (50.8)	19.6
History of hypercholesterolemia	4145 (31.3)	101 (23.2)	18.3
History of diabetes mellitus	2413 (18.2)	51 (11.7)	18.3
Current smoker	2515 (19.0)	132 (30.4)	26.7
Pre-stroke antithrombotic treatment[a]	5690 (43.0)	144 (33.3)	20.1
Admission systolic blood pressure, mean (SD)	148.7 ± 48.9	144.2 ± 27.5	13.6
Admission diastolic blood pressure, mean (SD)	82.9 ± 31.9	82.3 ± 17.4	2.4
Admission NIHSS score, median (IQR)[a]	16 (10 to 20)	15 (9 to 20)	6.1
Baseline ASPECTS, median (IQR)	8 (6 to 9)	8 (6 to 9)	7.9
Pre-stroke mRS score >1[a]	1631 (12.3)	35 (8.0)	14.3
Site of intracranial occlusion[a]			
Intracranial ICA	1608 (12.1)	70 (16.2)	20.6
M1	6558 (49.5)	196 (45.2)	
M2	1863 (14.1)	66 (15.3)	
Tandem	1455 (11.0)	57 (13.2)	
Vertebro baslilar	1015 (7.7)	18 (4.1)	
Isolated extracranial ICA	308 (2.3)	12 (2.8)	
Others/multiple	438 (3.3)	14 (3.3)	
Intravenous thrombolysis[a]	6711 (50.7)	175 (40.3)	20.9
General anesthesia	3120 (23.6)	162 (37.4)	30.5
Stroke etiology			
Dissection	520 (3.9)	36 (8.4)	20.9
Cardioembolic	6038 (45.6)	164 (37.8)	
Large artery atherosclerosis	2040 (15.4)	81 (18.8)	
Carotid web	77 (0.6)	5 (1.2)	
Others/multiple/undetermined	4569 (34.5)	147 (33.9)	
Onset to imaging, min, median (IQR)	126 (91 to 180)	137 (100 to 191)	15.7
Onset to arterial puncture, median (IQR)	265 (197 to 348)	274 (210 to 362)	11.1

Note: Values are expressed as number (%) unless otherwise indicated. Values were calculated after handing missing data using multiple imputation procedure.

Abbreviations: ASD, absolute standardized difference; ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular therapy; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

[a]Included in propensity score.

(3.2%) received an in situ bolus of nimodipine (249 for intracranial vasospasm, 94 for cervical vasospasm and 88 for both; see study flowchart in Figure S1). Table 1 shows the patients' baseline characteristics, with missing values handled by multiple imputation, stratified by study group (see Table S1 for baseline characteristics before handling missing values). Several meaningful differences were observed between the two study groups; patients with vasospasm treated with intra-arterial nimodipine were younger, were

TABLE 2 Comparisons in clinical and procedural outcomes according to the occurrence of vasospasm requiring treatment with nimodipine after propensity score overlap weighting.

	Vasospasm treated with nimodipine			
	No ($n = 13,244$)	Yes ($n = 434$)	Effect size (95% CI)	p value
Clinical outcome				
Favorable outcome[a]	5772 (43.6)	170 (39.2)	0.80 (0.61 to 1.06)	0.11
Excellent outcome[b]	4018 (30.3)	110 (25.4)	0.78 (0.63 to 0.97)	0.023
90-day mortality	3119 (23.5)	117 (26.9)	1.19 (0.85 to 1.67)	0.30
Intracranial hemorrhagic complications				
Any ICH	5429 (41.0)	193 (44.4)	1.15 (0.93 to 1.43)	0.20
sICH	1337 (10.1)	43 (10.0)	0.98 (0.61 to 1.58)	0.95
PH	1701 (12.8)	65 (14.9)	1.18 (0.69 to 2.03)	0.54
24 h ASPECTS shift, mean (95% CI)	−0.42 (−1.79 to 0.95)	−0.56 (−1.51 to 0.38)	−0.14 (−1.72 to 1.43)[c]	0.86
24 h NIHSS score shift, mean (95% CI)	−3.39 (−4.41 to −2.38)	−2.56 (−3.67 to −1.45)	0.83 (0.29 to 1.37)[c]	0.003
Procedural outcomes				
Final mTICI score 2b, 2c or 3	11,130 (84.0)	366 (84.3)	1.02 (0.68 to 1.52)	0.91
Final mTICI score 2c–3	7627 (57.6)	230 (52.7)	0.83 (0.56 to 1.22)	0.34
Final mTICI score 3	5023 (37.9)	121 (27.8)	0.63 (0.42 to 0.93)	0.02
Procedural complication	649 (4.9)	36 (9.4)	1.96 (1.37 to 2.79)	<0.001
Perforations	213 (1.6)	11 (2.5)	1.58 (0.79 to 3.12)	0.19
Emboli in a new territory	440 (3.3)	29 (6.6)	2.05 (1.41 to 2.99)	<0.001
Number of passes, median (IQR)	2 (1 to 3)	3 (1 to 4)	1.36 (1.15 to 1.62)	<0.001

Note: Values *n* (%) are estimated in the propensity score overlap weighted cohort unless otherwise indicated.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; ICH, intracerebral hemorrhage; IQR, interquartile range; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma of type 1 and 2; sICH, symptomatic intracerebral hemorrhage.

[a]Prespecified primary outcome defined as a 90-day modified Rankin Scale (mRS) score of 0–2, or equal to pre-stroke mRS score.

[b]Defined as a 90-day mRS score of 0–1, or equal to pre-stroke mRS score.

[c]Baseline-adjusted mean difference. Descriptive parameters and effect sizes (odds ratio or mean difference) were calculated after handling missing values for variables included in the propensity score using multiple imputations.

more often current smokers, less frequently had a history of cardiovascular risk factors (hypertension, hypercholesteriolemia, diabetes) and were more frequently treated under general anesthesia.

Outcomes and vasospasm treated with nimodipine in the main analysis population

In the PSOW population, the observed difference between groups in the primary outcome was not significant (mRS score 0–2 at 3 months; odds ratio [OR] 0.80, 95% confidence interval [CI] 0.61–1.06; $p = 0.11$ [Table 2]). However, vasospasm requiring intra-arterial nimodipine was significantly associated with lower odds of excellent outcome at 3 months (OR 0.78, 95% CI 0.63–0.97), a reduced improvement of NIHSS score at 24 h (mean difference 0.83, 95% CI 0.29–1.37), a higher number of device passes (mean difference 1.36, 95% CI 1.15–1.62) and a higher risk of procedural complications (OR 1.96, 95% CI 1.37–2.79), related more particularly to a higher risk of emboli in a new territory (OR 2.05, 95% CI 1.41–2.99). Final complete recanalization after MT (defined as final mTICI score 3) was also less frequent in the vasospasm group (OR 0.63, 95% CI 0.42–0.93). In the PS-matched cohort, similar effect sizes were found, with the difference in primary outcome reaching the significance level (OR 0.79, 95% CI 0.63–0.99), even though only the association between vasospasm treated with nimodipine and per procedural complication occurrence remained significant (OR 1.88, 95% CI 1.17–3.03; Tables S2 and S3 and Figure S2). Regarding ICH, we did not detect any association between vasospasm treated with intra-arterial nimodipine use and any of the subtypes of ICH (any ICH, sICH and parenchymal hematoma).

In the vasospasm group, an angiographic response to in situ nimodipine administration was observed in 69.3% (255/368): 82.8% (77/93) in patients with isolated cervical vasospasm and 64.7% (178/275) in patients with intracranial vasospasm. Among patients in the vasospasm group, a favorable angiographic response to in situ nimodipine administration was associated with a high chance of favorable and excellent outcome (OR 1.84, 95% CI 1.13–3.00 and OR 1.88, 95% CI 1.07–3.27, respectively) using a mixed logistic regression model taking into account center as a random effect.

Sensitivity analysis restricted to patients with intracranial vasospasm

Similar results were found in the study sample restricted to patients with intracranial vasospasm (Table 3). In addition to the lower odds of excellent functional outcome and final mTICI score of 3, a significant association with lower odds of favorable outcome (OR 0.64, 95% CI 0.45–0.92) and reduced rates of excellent reperfusion (final mTICI score 2c–3; OR 0.58, 95% CI 0.36–0.91) was found in the vasospasm group.

Sensitivity analysis restricted to patients with cervical vasospasm

In the study sample restricted to patients with cervical vasospasm only, we did not find any significant association between vasospasm requiring nimodipine use and the investigated outcomes (Table 4).

DISCUSSION

Through this large multicenter registry study, we observed that the occurrence of vasospasm treated with nimodipine in situ administration was associated with comparable rates of favorable functional outcome but lower odds of excellent functional outcome after 3 months, and reduced chances of perfect recanalization (final mTICI score 3) and of early neurological improvement, along with an increased procedural risk. This was even more prominent in cases of intracranial vasospasm treated with nimodipine. In cases of intracranial vasospasm, significantly lower odds of both favorable and excellent outcomes were observed in addition to worse early neurological status, decreased rates of excellent (final mTICI score 2c–3) and perfect recanalization (final mTICI score 3) and increased procedural risks. By contrast, in cases of isolated cervical vasospasm, no significant association with outcome was detected. In all analyses, no association was found between an arterial vasospasm necessitating in situ nimodipine infusion and the occurrence of any type of ICH.

TABLE 3 Comparisons in clinical and procedural outcomes according to the occurrence of intracranial vasospasm requiring treatment with nimodipine after propensity score overlap weighting.

	Vasospasm treated with nimodipine			
	No	Yes		
	(*n* = 13,244)	(*n* = 249)	Effect size (95% CI)	*p* value
Clinical outcome				
Favorable outcome[a]	5772 (43.5)	82 (33.1)	0.64 (0.45 to 0.92)	0.017
Excellent outcome[b]	4018 (30.3)	54 (21.6)	0.63 (0.44 to 0.92)	0.016
90-day mortality	3119 (23.6)	67 (27.0)	1.20 (0.89 to 1.64)	0.23
Intracranial hemorrhagic complications				
Any ICH	5429 (41.0)	117 (47.0)	1.28 (0.96 to 1.71)	0.095
sICH	1337 (10.1)	27 (10.7)	1.04 (0.51 to 2.13)	0.90
PH	1701 (12.8)	40 (16.2)	1.30 (0.75 to 2.26)	0.34
24 h ASPECTS shift, mean (95% CI)	−0.43 (−1.84 to 0.97)	−0.74 (−1.75 to 0.27)	−0.31 (−1.83 to 1.22)[c]	0.69
24 h NIHSS shift, mean (95% CI)	−3.36 (−4.64 to −2.08)	−1.63 (−3.11 to −0.15)	1.73 (0.95 to 2.52)[c]	<0.001
Procedural outcomes				
Final mTICI score 2b, 2c or 3	11,130 (84.0)	200 (80.4)	0.78 (0.53 to 1.15)	0.21
Final mTICI score 2c–3	7627 (57.6)	110 (44.0)	0.58 (0.36 to 0.91)	0.020
Final mTICI score 3	5023 (38.0)	59 (23.6)	0.50 (0.28 to 0.90)	0.021
Procedural complication	649 (4.9)	29 (11.5)	2.54 (1.54 to 4.20)	<0.001
Perforations	211 (1.6)	7 (2.7)	1.68 (0.52 to 5.44)	0.39
Emboli in a new territory	437 (3.3)	22 (8.9)	2.82 (1.85 to 4.29)	<0.001
Number of passes	2 (1 to 3)	3 (2 to 4)	1.49 (1.24 to 1.79)	<0.0.001

Note: Values *n* (%) are estimated in the propensity score overlap weighted cohort unless otherwise indicated.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; ICH, intracerebral hemorrhage; IQR, interquartile range; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma of type 1 and 2; sICH, symptomatic intracerebral hemorrhage.

[a]Prespecified primary outcome defined as a 90-day modified Rankin Scale (mRS) score of 0–2, or equal to pre-stroke mRS score.

[b]Defined as a 90-day mRS score of 0–1, or equal to pre-stroke mRS score.

[c]Baseline-adjusted mean difference. Descriptive parameters and effect sizes (odds ratio or mean difference) were calculated after handling missing values for variables included in the propensity score using multiple imputations.

TABLE 4 Comparisons in clinical and procedural outcomes according to the occurrence of cervical vasospasm requiring treatment with nimodipine after propensity score overlap weighting.

	Vasospasm treated with nimodipine			
	No ($n = 13,244$)	Yes ($n = 94$)	Effect size (95% CI)	*p* value
Clinical outcome				
Favorable outcome[a]	5772 (43.5)	48 (51.3)	1.37 (0.63 to 2.98)	0.42
Excellent outcome[b]	4018 (30.3)	31 (33.4)	1.15 (0.72 to 1.85)	0.55
90-day mortality	3119 (23.6)	27 (28.7)	1.30 (0.54 to 3.08)	0.55
Intracranial hemorrhagic complications				
Any ICH	5429 (41.0)	31 (32.8)	0.70 (0.44 to 1.11)	0.13
sICH	1337 (10.1)	10 (10.7)	1.06 (0.42 to 2.68)	0.90
PH	1701 (12.8)	12 (12.7)	0.98 (0.45 to 2.16)	0.97
24 h ASPECTS shift, mean (95% CI)	−0.43 (−1.78 to 0.93)	−0.51 (−1.55 to 0.54)	−0.08 (−1.75 to 1.59)[c]	0.92
24 h NIHSS shift, mean (95% CI)	−3.76 (−5.01 to −2.51)	−3.48 (−4.95 to −2.01)	0.28 (−0.42 to 0.98)[c]	0.41
Procedural outcomes				
Final mTICI score 2b, 2c or 3	11,130 (84.0)	81 (86.1)	1.18 (0.48 to 2.92)	0.72
Final mTICI score 2c–3	7627 (57.6)	60 (63.7)	1.29 (0.86 to 1.94)	0.21
Final mTICI score 3	5023 (37.9)	28 (29.5)	0.68 (0.42 to 1.11)	0.13
Procedural complication	649 (4.9)	3 (3.4)	0.70 (0.32 to 1.50)	0.35
Perforations	213 (1.6)	0	NA	NA
Emboli in a new territory	440 (3.3)	3 (3.4)	1.01 (0.47 to 2.17)	0.98
Number of passes	2 (1 to 3)	2 (1 to 3)	1.08 (0.87 to 1.34)	0.48

Note: Values *n* (%) are estimated in the propensity score overlap weighted cohort unless otherwise indicated.

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence intervals; ICH, intracerebral hemorrhage; IQR, interquartile range; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma of type 1 and 2; sICH, symptomatic intracerebral hemorrhage.

[a]Pre-specified primary outcome defined as a 90-day mRS score of 0–2, or equal to pre-stroke mRS score.

[b]Defined as a 90-day mRS score of 0–1, or equal to pre-stroke mRS score.

[c]Baseline-adjusted mean difference; Descriptive parameters and effect sizes (odds ratio or mean difference) were calculated after handling missing values for variables included in the propensity score using multiple imputations.

One interesting point in this study was the incidence of vasospasm treated with nimodipine, which was 3.2% (434/13678) in the global registry population. This appears to be in line with the literature [6–10]. Indeed, although available specific data are very limited, the incidence of iatrogenic vasospasm during MT for LVOS has been reported to be between 3.9% and 23%. However, it must be underlined that in the great majority of previous publications, there was limited information regarding its potential prognostic impact and its management. In the present study, we chose to focus on vasospasm perceived to be severe enough to prompt the operator

to administer nimodipine. Of course, this point can be debated and might be a source of bias. However, given the absence of a standardized definition and grading scale for arterial vasospasm, standard treatment guidelines and even established knowledge of the impact of iatrogenic vasospasm and nimodipine use in the setting of EVT for LVOS, we assumed that this choice allowed the identification of a relatively homogeneous group of patients [11]. Indeed, we presumed that operators decided to administer nimodipine in patients with vasospasm that was assumed to be severe enough to require a specific treatment. Vasospasm severity was likely determined by an angiographically severe arterial stenosis and/or a downstream substantial hemodynamic impact of this stenosis.

Angiographically detected arterial vasospasm during MT is usually deemed secondary to a reaction of the arterial wall due to device passes and/or navigation into cervical and/or intracranial arteries. However, its diagnosis can be challenging [21, 22]. In particular, it is sometimes difficult to exclude alternative causes of arterial narrowing or re-occlusion during an MT procedure, including a residual thrombus or an underlying arterial wall disease (atherosclerosis, dissection, vasculitis) [23]. In such a situation, vasodilator administration may be used as a therapeutic or diagnostic test [21]. The absence of angiographic response to nimodipine may reorientate diagnosis toward an underlying arterial wall disease. Therefore, we must acknowledge that some patients in the vasospasm group eventually presented an alternative cause of arterial stenosis. This likely explains the increased use of rescue therapies in the vasospasm group (aspirin, glycoprotein IIb/IIIa inhibitors, intracranial stenting or angioplasty). Given the absence of standardized guidelines, the interpretation of arterial lesions and the decision to administer additional rescue therapy remain at operator discretion, on a case-by-case basis. This likely accounts for the increased procedural risk in this subgroup. Nevertheless, no statistical differences in LVOS etiologies were observed between vasospasm and no-vasospasm groups. In addition, an angiographic enlargement of the arterial lumen after nimodipine infusion was observed in most patients, reflecting reliable identification of arterial vasospasm by the operator.

Nimodipine is frequently used in the treatment of iatrogenic vasospasm, despite the limited available data. Intra-arterial nimodipine has been used for decades in the treatment of iatrogenic or post-aneurysmal subarachnoid hemorrhage vasospasm, yielding satisfactory results [4, 5, 24]. This approach has been widely transposed to the context of MT. However, in this setting, its administration requires specific attention to its safety and efficacy profiles. In particular, vasodilator infusion can induce a systemic hypotension potentially harmful in the context of an acute ischemic stroke [25]. Nimodipine bolus must be injected cautiously with close monitoring of blood pressure, and potentially combined with vasopressor drugs to compensate for and avoid dangerous drops [26]. In the present study, we could not determine whether the impact on outcomes was attributable to the arterial vasospasm itself or the administration of nimodipine. However, given the concerning signals toward worse prognosis, efforts should be made to: (i) avoid the occurrence of iatrogenic vasospasm during EVT, especially in intracranial arteries; (ii) evaluate the benefit–risk ratio of nimodipine use in this indication; and (iii) cautiously compensate for the hypotensive side effect of nimodipine. There undoubtedly remain situations where in situ nimodipine is necessary and helpful. However, the present study suggests the need for some caution around iatrogenic vasospasm and its treatment. Similarly, as with post-aneurysmal subarachnoid hemorrhage vasospasm, alternative techniques or agents such as balloon angioplasty or milrinone merit investigation [4, 5, 27].

Given the fact that it cannot be determined whether it was the vasospasm itself or its treatment with nimodipine which impaired outcomes, one major conclusion that should be drawn from this work is the need to prevent iatrogenic vasospasm if possible. Device design improvements, efforts to improve the MT technique in order to achieve optimal recanalization with the minimum number of passes and shorter endovascular procedures, as well as proper evaluation of the required sizes for the intracranial aspiration catheter or stent retriever, might be considered. Notably, the increased number of MT passes in the vasospasm group can be interpreted either as a cause or a consequence of vasospasm. Vasospasm and its consequences might partly explain the reported decreasing odds of favorable outcomes associated with repeated MT passes [28].

The main limitation of this study was the absence of a control group in whom vasospasm occurred without the use of nimodipine, which would allow us to differentiate the impact of nimodipine from the impact of vasospasm itself. However, as discussed above, such a study design would not be possible or ethical. Consequently, we cannot determine whether the outcome alterations were due to arterial vasospasm, intra-arterial nimodipine or both. Nevertheless, we believe this study has identified an important signal that the occurrence of vasospasm requiring pharmacological therapy could be harmful and efforts should be considered to reduce the risk of facing this iatrogenic issue. Additionally, this was a retrospective study and consequently it has inherent biases, including missing data. In the absence of centralized evaluation of digital subtraction angiography, vasospasm diagnosis was locally adjudicated. Given the absence of guidelines, there may have been heterogeneity in vasospasm detection and management (timing of administration, administered dose, quickness of the infusion, hemodynamic compensation). The presence or absence of vasospasm relied on operator perception as well as the need for a specific treatment with intra-arterial nimodipine. Given the possible difficulties in angiographic diagnosis of vasospasm and the potential differential diagnoses (alternative stenosis etiologies), we cannot exclude biases. However, MT procedures were performed in large comprehensive stroke centers by experienced operators. Additional limitations include the fact that the angiographic response to nimodipine was not widely available in this study, and that, given the limited number of patients in the vasospasm group especially in secondary analyses, the statistical analyses may lack power.

In conclusion, we found that arterial vasospasm requiring intra-arterial treatment with nimodipine in the setting of an MT procedure

was associated with worse clinical and angiographic outcomes and increased procedural complication rates. Intracranial vasospasm treated with in situ nimodipine, in particular, was associated with worse outcomes whereas cervical vasospasm was not. Although this study could not formally differentiate whether the negative consequences were due to the vasospasm itself, its treatment with in situ nimodipine, or both, it seems that there is an important signal toward a substantial clinical impact of iatrogenic vasospasm during MT. Further studies are required to optimize and standardize both prevention and treatment of iatrogenic arterial vasospasm occurring during MT.

AUTHOR CONTRIBUTIONS

Serine Ferhat: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing. **Guillaume Bellanger:** Writing – review and editing; data curation; investigation. **Malgorzata Milnerowicz:** Investigation; writing – review and editing; data curation. **Maeva Kyheng:** Writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; software; data curation. **Julien Labreuche:** Writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; data curation. **Igor Sibon:** Conceptualization; writing – review and editing. **Mehdi Khobzi:** Data curation; writing – review and editing. **Joe-Marie Abousleiman:** Data curation; writing – review and editing. **Dan-Adrian Popica:** Writing – review and editing; data curation. **Solene Moulin:** Writing – review and editing; data curation. **Cyril Dargazanli:** Data curation; writing – review and editing. **Arturo Consoli:** Writing – review and editing; data curation. **Omer Eker:** Data curation; writing – review and editing. **Louis Veunac:** Writing – review and editing; data curation. **Kevin Premat:** Writing – review and editing; data curation. **Benjamin Gory:** Writing – review and editing; data curation. **Jean-Christophe Gentric:** Writing – review and editing; data curation. **Ricardo Moreno:** Writing – review and editing; data curation. **Wagih Ben Hassen:** Data curation; writing – review and editing. **Maxime Gauberti:** Data curation; writing – review and editing. **Raoul Pop:** Writing – review and editing; data curation. **Aymeric Rouchaud:** Writing – review and editing; data curation. **Romain Bourcier:** Data curation; writing – review and editing. **Bertrand Lapergue:** Writing – review and editing; data curation; methodology; conceptualization; investigation; validation; formal analysis; project administration; supervision; resources. **Gaultier Marnat:** Writing – review and editing; data curation; supervision; conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; project administration; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare non conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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