

Infarct in a New Territory after Treatment Administration in the ESCAPE Randomized Controlled Trial

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ABSTRACT

Background and purpose: Infarct in a new previously unaffected territory (INT) is a potential complication of endovascular treatment. We applied a recently proposed methodology to identify and classify INTs in the ESCAPE randomized controlled trial.

Methods: The core lab identified INTs on 24-hr follow-up imaging, blinded to treatment allocation, after assessing all baseline imaging. INTs were classified into 3 types (I-III) and 2 subtypes (A/B) based on size and if catheter manipulation was likely performed across the vessel territory ostium. Logistic regression was used to understand the effect of multiple a priori identified variables on INT occurrence. Ordinal logistic regression was used to analyse the effect of INTs on modified Rankin Scale shift at 90 days.

Results: From 308 patients included, 14 INTs (4.5% overall; 2.8% on follow-up NCCT, 11.7% on follow-up MRI) were identified [5.0% in endovascular treatment arm vs. 4.0% in control arm ($p=0.7$)]. Use of intravenous alteplase was associated with a 68% reduction in the odds of INT occurrence (3.0% with vs. 9.1% without, Odds ratio [OR] 0.32, 95% confidence interval [CI] 0.11-0.96; adjusted for age, sex and treatment type). No other variables were associated with INTs. INT occurrence was associated with reduced probability of good clinical outcome (common OR 0.25, 95% CI 0.09-0.74, adjusted for age, type of treatment and follow-up scan).

Conclusions: INTs are uncommon, detected more frequently on follow-up MRI, and affect clinical outcome. In experienced centers, endovascular treatment is likely not causal while intravenous alteplase may be therapeutic.

Clinical Trial Registration – URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01778335.

INTRODUCTION

Endovascular treatment is now the standard of care for acute large vessel ischemic stroke in the anterior circulation.¹⁻⁵ Infarct in a New Territory (INT) is a potential complication of endovascular treatment, and implies that the intervention results in a new infarct in a territory that was unaffected by the original occlusion.⁶ An example of this would be an ipsilateral anterior cerebral artery (ACA) infarct in a patient who received endovascular treatment for a mid-M1 occlusion in the middle cerebral artery (MCA). INT can be identified on a follow-up non-contrast CT (NCCT) scan or diffusion-weighted MRI.

There is a need for consistent reporting of such adverse events in clinical trials to facilitate better understanding of the complications of endovascular therapy.^{7, 8} We recently proposed a methodology for the documentation of INT after the endovascular procedure.⁶ This classification takes into account variations in vascular anatomy and the location of the thrombus, using information on the pre-procedure non-invasive vascular imaging, end-of-procedure angiography images, and the location of infarcts on follow-up imaging. INTs are classified on the basis of size as well as catheter manipulation across the ostium of the arterial territory (Table I, Online Supplement, please see <http://stroke.ahajournals.org>).

We applied this methodology to identify and classify INTs in the ESCAPE (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times) trial of endovascular stroke treatment.

METHODS

ESCAPE was a prospective, multicentre, randomized clinical trial (NCT01778335), the methodology of which has been detailed in prior publications.^{2,9} The trial involved 22 centres in Canada (11), the United States (6), Korea (3), the United Kingdom (1), and Ireland (1). All patients received a non-contrast CT (NCCT) head and a CT angiography (CTA, preferably multiphase). Inclusion criteria for the trial, in brief, were: acute ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score >5; symptom onset within 12 hours of presentation; no pre-morbid disability; a small infarct core defined as an Alberta Stroke Program Early CT Score (ASPECTS) >5 on NCCT head; internal carotid artery (ICA), M1, or functional M1 occlusion, and moderate to good collaterals on CTA. Patients randomized into the treatment arm received standard care plus endovascular treatment with available thrombectomy devices. The use of retrievable stents and suction through a balloon guide catheter (BGC) in the relevant internal carotid artery during thrombus retrieval were recommended. Aggressive target times were chosen – 60 minutes or less from study NCCT to groin puncture and 90 minutes or less from study NCCT to first reperfusion. Patients randomized into the control arm received intravenous alteplase (0.9 mg/kg body weight) or standard stroke care as per established guidelines. For this per-protocol analysis, treatment was defined as use of a guide catheter across the arch at least once; patients randomized to the endovascular arm not receiving that treatment were therefore excluded from analysis.

The central core lab identified INTs on 24-hr follow-up imaging (Magnetic Resonance Diffusion Weighted Imaging [MR-DWI] if available; non-contrast CT if MRI was not available). The follow-up imaging was compared with baseline parenchymal and vascular imaging and procedural angiography. The core lab flagged all infarcts located outside the immediate territory of the vessel implicated in the presenting stroke using the new

classification of INT (Table I, please see <http://stroke.ahajournals.org>). The diameter of these infarcts was measured and the infarcts were classified into one of 3 types (I-III) and 2 subtypes (A or B; for the endovascular arm only) as in Table 1. The number and proportion of INTs in each category were reported in the endovascular and control arms of the trial. We analysed the effect of *a priori* identified variables such as age, sex, history of congestive heart failure, atrial fibrillation on anticoagulation, baseline International Normalized Ratio (INR), baseline Partial Thromboplastin Time (PTT), presence of extra-cranial carotid disease, baseline site of occlusion (middle vs. internal carotid artery segment), baseline clot burden score (trichotomized as 0-4, 5-7 and 8-10; higher scores indicate lower clot burden),¹⁰ use of intravenous alteplase at baseline, and time from stroke symptom onset to randomization on development of INT using logistic regression. We also analysed the use of balloon guide catheters or stent retrievers in the endovascular arm and development of INT. Finally, we analysed the effect of INTs on the primary clinical outcome in the ESCAPE trial i.e. modified Rankin Scale (mRS) shift at 90 days, using ordinal logistic regression after adjusting for age, sex, and treatment type. The proportional odds assumption was tested using Brant's Wald test. Sensitivity analyses were carried out to analyse if follow-up imaging modality i.e. non-contrast CT vs. MRI affected results. Statistical analysis was carried out in Stata/MP version 14.0 (StataCorp LP). Statistical significance was assessed two-sided at $\alpha \leq 0.05$ in all analyses.

RESULTS

160 (51.8%) patients received endovascular treatment when compared to 149 (48.2%) patients in the control arm. One patient in the endovascular treatment arm did not have follow-up imaging and was therefore excluded from further analysis. Of the 308 patients included in the analysis, INTs were assessed using MR-DWI in 59 (19.2%) patients. A total

of 14 INTs (4.5% overall), 5.0% (n=8) in the endovascular treatment arm and 4.0% (n=6) in the control arm (p=0.7), were identified. Distribution of INTs stratified by follow-up imaging modality and treatment type is shown in Figure 1. Distribution of INTs as per the new classification (Table I, please see <http://stroke.ahajournals.org>) in the endovascular treatment arm versus the control arm of the trial is shown in Table 1.

Use of intravenous alteplase at baseline was associated with a 68% reduction in the odds of occurrence of INTs on follow-up (3.0% vs. 9.1% without intravenous alteplase, OR 0.32, 95% CI 0.11-0.96; adjusted for age, sex and treatment type). No other predictor variables were associated with occurrence of INTs on follow-up in univariate (Table 2) or multi-variable analysis (Table II, Online Supplement, please see <http://stroke.ahajournals.org>). In the endovascular treatment arm, the use of a balloon guide catheter (p=0.325) or stent retriever (p=0.983) was not associated with reduced occurrence of INTs. Occurrence of INTs on follow-up imaging was associated with a significant reduction in odds of good clinical outcome (improvement of 1 point on the mRS scale) after adjusting for age, treatment type and type of follow-up scan (MRI vs. CT): Common OR 0.25, 95% CI 0.09-0.74, Brant test p=1.0 (Table 3).

In sensitivity analyses looking at the effect of variability in follow-up imaging modality on estimates, the use of MRI was more common in the endovascular treatment arm than in the control arm (25.2% vs. 12.7%, p<0.01). The rate of detection of INTs ranged from 2.8% on follow-up NCCT to 11.7% on follow-up MRI. There was no statistically significant difference in detection of INTs between endovascular treatment and control arm when using follow-up non-contrast CT (3.1% vs. 2.5% respectively, p=1.0) or MRI (12.5% vs. 10.5%

respectively, $p=1.0$). Use of intravenous alteplase at baseline was associated with a 66% reduction in the odds of occurrence of INTs on follow-up (OR 0.34, 95% CI 0.11-1.00; $p=0.05$, adjusted for age, sex, treatment type and type of follow-up imaging). None of the other predictor variables were associated with occurrence of INTs on follow-up non-contrast CT or MRI ($p>0.05$).

DISCUSSION

We found that the occurrence of INTs in the ESCAPE trial was low (4.5% overall) while large INTs were rare (1.3%). We noted no difference in occurrence of INTs between endovascular treatment and control arms of the trial. Even within the endovascular treatment arm, 6/8 INTs were Type B i.e. the guide catheter was less likely to have been manipulated past the ostium of the affected arterial territory in these INTs (Table 1). Our results suggest that the occurrence of INTs may not be related to the endovascular procedure, especially in experienced centres. Interestingly, we found that the administration of intravenous alteplase was associated with significantly fewer INTs on follow-up imaging.

With the success of the recent endovascular treatment trials, an issue of interest in the stroke community is the safety of the procedure itself. Endovascular treatment is an invasive procedure; as such it has been assumed that the procedure is likely to dislodge thrombi into as yet unaffected arterial territories, causing INTs. The MR CLEAN trial reported 13 cases (5.6%) of new ischemic stroke in a different vascular territory in the interventional arm compared to 1 case (0.4%) in the control arm, though this was based on clinical signs only (systematic INT analysis is in preparation).¹ EXTEND-IA reported 2 cases (6%) of

embolization into a different vascular territory identified on neuroimaging in the interventional arm,⁵ and REVASCAT reported 5 (4.9%) of cases of distal embolization in a different territory.⁴ This outcome was not among the adverse events reported by SWIFT-PRIME trial.³ Although the ESCAPE trial initially reported 32 infarcts as INTs, a re-review of imaging using the new classification in Table 1 resulted in our trial reporting only 14 INTs; the remaining infarcts were explainable as pre-procedural or likely to be in the primary vascular territory involved. This analysis of INTs within the ESCAPE trial using a standardized classification has not only shown that INTs are uncommon but also that they are less likely to be a complication of the endovascular procedure itself. This is further substantiated by the occurrence of INTs regardless of the use of balloon guide catheters or stent retrievers in our analysis.

Concerns have also been raised about intravenous alteplase causing INTs by disintegrating potentially pre-existing thrombi within the cardiac or large arterial system and causing early recurrent ischemic stroke.¹¹ Our analysis refutes this hypothesis by showing that administration of intravenous alteplase was associated with a reduction in the odds of occurrence of INTs by 68% on average. Our analysis also shows that no other variable of interest was associated with the occurrence of INTs. It could therefore be hypothesized that thrombi causing INTs may occur before, with, or after the index ischemic stroke event potentially as a result of the same pathology. Intravenous alteplase is possibly therapeutic, perhaps by dissolving not just the target thrombus but also any new thrombi that may have formed or embolized during this time. This could potentially be further examined in a randomized controlled trial of intravenous alteplase plus endovascular therapy versus endovascular therapy alone.

INTs are likely to reduce the chance of good clinical outcome in patients with acute ischemic stroke, with larger INTs likely to do so more than smaller INTs (data not shown; Figure 2). The two established treatment modalities for acute ischemic stroke i.e. endovascular treatment and administration of intravenous alteplase are likely not causal. Moreover intravenous alteplase may reduce occurrence of INTs, thus improving the chance of good clinical outcome in these patients. A limitation of our study is that a majority (80%) of INTs were identified on CT imaging. Since MRI is more sensitive than CT in picking up acute infarcts, we may have under-estimated the true prevalence of INTs. Nonetheless, in sensitivity analyses adjusting for type of follow-up imaging modality, our results with regards to treatment-type differences (endovascular treatment vs. control) and use of intravenous alteplase remain valid. Finally, given the post hoc nature of our analysis, our results will need to be replicated in other studies.

In conclusion, INTs are uncommon but affect clinical outcome and are likely an epiphenomena of the acute ischemic stroke process, rather than a complication of ischemic stroke treatment, especially in experienced centers.

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BKM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors fulfil ICMJE criteria for authorship.

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Cheemun Lum, Jennifer Mandzia, Stephen Phillips, Oh Young Bang, Mohammed Almekhlafi, Shelagh Coutts, Philip Barber, Tolulope Sajobi, and Muneer Eesa all have nothing to disclose.

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FIGURE LEGENDS

Figure 1: Distribution of Infarcts in New Territory stratified by follow-up imaging modality (non-contrast CT vs. MRI), treatment arm and intravenous alteplase administration.

Figure 2: An example of a Type III-B Infarct in New Territory (INT): a new infarct >20mm in size, contralateral to the procedure in a patient who presented with a left M1 occlusion.

(A) Baseline CTA showing the left M1 occlusion; (B) and (C) axial NCCT slices demonstrating the new infarct indicated by the arrows. The catheter was less likely to have been manipulated across the ostium of the new territory during the procedure, and new embolization from a proximal source cannot be excluded.

TABLES

Table 1: Classification of Infarct in New Territory (INT) in the ESCAPE trial (n=308).

INT Classification*	Endovascular Arm (n=159)	Control Arm (n=149)
Type I-A	1	1
Type I-B	0	
Type II-A	0	3
Type II-B	4	
Type III-A	1	2
Type III-B	2	
Total	5.03%	4.02%

*Adapted from a previous publication and based on size of infarct (types I to III) and whether catheter was likely manipulated past ostium of new territory (A – yes, B – no)⁶

Table 2: Variables associated with occurrence of Infarct in New Territory (INT) in the ESCAPE trial.

		Univariate Analysis		Multivariable Analysis ¶	
		Odds	95% Confidence	Odds	95% Confidence
Predictor Variable		Ratio	Interval	Ratio	Interval
Age (per year)		1.02	0.98-1.06	1.01	0.97-1.06
Sex (male vs. female)		1.23	0.42-3.63	1.1	0.36-3.31
History of Congestive Heart Failure (Yes vs. No)		1.59	0.43-5.94		
History of Atrial Fibrillation on Anticoagulation (Yes vs. No)		1	0.99-1.01		
International Normalized Ratio (per 1 point)		1.24	0.24-6.32		
Partial Thromboplastin Time (per 1 second)		1.06	1.00-1.14		
Extra-cranial Carotid Disease (Yes vs. No)		1.84	0.59-5.68		
Site of Occlusion (Middle Cerebral artery vs. Internal Carotid Artery)		0.47	0.16-1.41		
Clot Burden Score	0-4 (Reference)	1	-		
	5 to 7	0.96	0.3-3.13		
	8 to 10	0.56	0.11-2.99		
Endovascular Treatment (Yes vs. No)		1.26	0.43-3.73	1.17	0.39-3.49

Intravenous Alteplase (Yes vs. No)	0.31*	0.11-0.92*	0.32*	0.11-0.96*
Symptom Onset to Randomization Time (in mins)	1	0.99-1.00		

* Statistically significant ($p \leq 0.05$), ¶ - Age, Sex and Treatment type included in the model although not significant in univariate analysis.

Table 3: Association of Infarct in New Territory (INT) with primary clinical outcome in the ESCAPE trial (shift in modified Rankin Scale at 90 days) after adjusting for age and treatment type.

Predictor Variable	Common Odds	
	Ratio¶	95% Confidence Intervals
Age (per year)	0.96	0.95-0.97
Endovascular Treatment (Yes vs. No)	2.9	1.90-4.42
Infarct in New Territory (Yes vs. No)*	0.25	0.09-0.74
Follow-up scan type (MRI vs. CT)*	1.75	1.04-2.95

¶ Improvement of 1 point on the mRS scale. * Test of interaction between Infarct in new territory and Follow-up scan type in determining clinical outcome was non-significant.