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Final infarct volume estimation on 1-week follow-up MR imaging is feasible and is dependent on recanalization status

Mark Krongold [a,b,c], Mohammed A. Almekhlafi [a,b,d], Andrew M. Demchuk [a,b,e], Shelagh B. Coutts [a,b,e], Richard Frayne [a,b,c,*], Armin Eilaghi [a,b,c]

[a] Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[b] Seaman Family Centre, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta, Canada
[c] Biomedical Engineering, University of Calgary, Calgary, Alberta, Canada
[d] King Abdulaziz University, Jeddah, Saudi Arabia
[e] Calgary Stroke Program, Foothills Medical Centre, Calgary, Alberta, Canada

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ABSTRACT

Purpose: We aim to characterize infarct volume evolution within the first month post-ischemic stroke and to determine the effect of recanalization status on early infarct volume estimation.
Methods: Ischemic stroke patients recruited for the MONITOR and VISION studies were retrospectively screened and patients who had infarcts on diffusion-weighted imaging (DWI) at baseline and had at least two follow-up MR scans ($n = 56$) were included. Pre-defined target imaging time points, obtained on a 3-T MR scanner, were 12 hours (h), 24 h, 7 days, and ≥30 days post-stroke. Infarct tissue was manually traced blinded to the images at the other time points. Infarct expansion index was calculated by dividing infarct volume at each follow-up time point by the baseline DWI infarct volume. Recanalization was assessed within 24 h post-stroke. Correlation and statistical comparison analysis were done using the Spearman, Mann–Whitney, and Kruskal–Wallis tests.
Results: Follow-up infarct volumes were positively correlated with the baseline infarct volume ($\rho > 0.81$; $p < 0.001$) where the strongest correlation existed between baseline and 7-day post-stroke infarct volumes ($\rho = 0.92$; $p < 0.001$). The strongest correlation among the follow-up imaging was found between infarct volumes 7-day post-stroke and ≥30-day time points ($\rho = 0.93$; $p < 0.001$). Linear regression showed a close-to unity slope between 7-day and final infarct volumes (slope = 1.043; $p < 0.001$). Infarct expansion was higher in the non-recanalized group than the recanalized group at the 7-day ($p = 0.001$) and ≥30-day ($p = 0.038$) time points.
Conclusions: Final infarct volume can be approximated as early as 7 days post-stroke. Final infarct volume approximation is significantly associated with recanalization status.

1. Introduction

Final infarct volume is a clinically useful measure associated with the stroke functional outcome (Lev et al., 2001). It is also linked to multiple other baseline radiological scores such as the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (Coutts et al., 2004), clot burden score (Tan et al., 2009), and clinical parameters, e.g., National Institute of Health Stroke Scale (NIHSS) (Saver et al., 1999). Final infarct volume depicts the extent of infarct growth and provides a gold standard criterion to study the efficacy of treatment/management strategies (Olivot et al., 2008; Eilaghi et al., 2014). While infarct progression is widely accepted to be a dynamic process, final infarct volume has been measured at different time points in these various studies, such as after 90 days (Warach et al., 2000; Warach et al., 2006; Davis et al., 2008), 30 days, (Olivot et al., 2008; Hacke et al., 2005; Furlan et al., 2006) and 5 days (Wheeler et al., 2013; Lemmens et al., 2013). There is a tendency to use earlier time points in more recent Phase 2 clinical trials and proof-of concept studies to minimize patient drop out, minimize stroke-related complications, and reduce the overall study costs. Gaudinski et al. (2008) for example, showed that the infarct volume stabilized 30 days post-stroke compared to 3 months in 19 patients with acute stroke.

* Corresponding author at: Seaman Family Centre, Foothills Medical Centre, 1403 29 Street NW, Calgary, Alberta T2N 2T9, Canada. Tel.: +1 403 944 8321; fax: +1 403 270 7907.
E-mail address: markkrongold@gmail.com (M. Krongold), malmekhl@ucalgary.ca (M.A. Almekhlafi), ademchuk@ucalgary.ca (A.M. Demchuk), scoutts@ucalgary.ca (S.B. Coutts), rfrayne@ucalgary.ca (R. Frayne), aeilaghi@ucalgary.ca (A. Eilaghi).

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Recanalization is among the strongest predictors of clinical outcome and final infarct volume in patients with acute ischemic stroke (Rha, and Saver, 2007). Early recanalization is believed to improve the chance of survival in affected ischemic tissues. Therefore, it is reasonable to assume that recanalization status would change the infarct volume evolution. However, the exact association of infarct volume evolution with recanalization has not been quantified, particularly at the sub-acute stage. For example, it is unclear whether recanalization status affects the estimation of infarct volume size at the sub-acute stage. Recently, a linear association was reported between infarct volumes at the sub-acute (3–6 days) and chronic (>30 days) stages with both time points showing equivalent predictive value of the clinical outcome in a highly recanalized (68%) cohort (Tourdias et al., 2011). However, prediction of the final infarct volume at the early time points may be more useful in patients who do not recanalize. In such patients, prolonged follow-up is difficult to attain, as these patients are prone to clinical complications.

This study aimed to characterize infarct volume expansion in a population of patients with an intracranial occlusion who are at risk for infarct expansion after the baseline scans. We hypothesized that scanning at 7 days would be a good surrogate of final infarct volume.

2. Methods

2.1. Patient selection

This is a retrospective analysis of patients who enrolled in the MONITOR (Simon et al., 2005) or VISION (Coutts et al., 2008; Coutts et al., 2011) studies. The institutional research ethics board approved both studies and patients or their surrogates provided written informed consent. The VISION and MONITOR studies were imaging studies completed in acute ischemic stroke and TIA patients. A subset of patients with evidence of a middle cerebral artery (MCA) occlusion had serial imaging completed as part of these studies. Patients were eligible for the current analysis if they had baseline imaging including diffusion weighted (DWI) imaging (<6 h), follow-up fluid attenuated inversion recovery (FLAIR) imaging (>30 days), and at least one further FLAIR imaging at a pre-defined time point between these 2 scans. All patients had evidence of an MCA occlusion on MRA.

2.2. Image acquisition

Pre-defined target imaging time points included: baseline (<6 h), 12 h, 24 h, 7 days, and >30 days after stroke onset. Images were obtained using a 3 T MRI (Signa VH/*i*; GE Healthcare) with high performance gradients (40 mT/m; 184 μs rise time) using a standard quadrature head coil and established stroke imaging protocols (Lauzon et al., 2006). Single-shot echo-planar imaging was used for diffusion-weighted images ($b = 0$ s mm^{-2} and isotropic $b = 1000$ s mm^{-2}; repetition time = 9000 ms; echo time = min [80–90 ms]; 240 mm field-of-view; 5.0 mm slice thickness with a 0 or 2 mm gap). ADC maps were derived from the $b = 0$ s mm^{-2} and b = 1000 s mm^{-2} images (DeVetten et al., 2010). FLAIR images were acquired with repetition time = 9002 ms; echo time = 140 ms; inversion time = 2250 ms; 240 mm field-of-view; 3.0 mm slice thickness; and 2.0 mm gap. MR angiography (MRA) was performed using 3D time-of-flight imaging using repetition time = 22 ms; echo time = 3.3 ms; flip angle = 15°; acquisition bandwidth of ±12.5 kHz; and a 320 × 256 × 44 mm acquired volume.

2.3. Image analysis

Images were assessed blinded to patient identifiers and time points by tracing lesions on DWI and FLAIR images in CEREBRA medical imaging software, (Gobbi et al., 2012) (M.K., A.E.) and edited using MIPAV (Medical Image Processing, Analysis, and Visualization, BIRSS; NIH, Bethesda, Maryland, USA). Acute lesions were identified on baseline DWI while follow-up lesions were identified on FLAIR images. The infarct regions were confirmed by a stroke neurologist (M.A.). Infarct expansion index was calculated by finding the ratio of the infarct volume on FLAIR imaging at each time point to the baseline DWI infarct volume. To assess the effect of initial infarct volume, the cohort was then split into patients with large (≥10 ml; top 20th percentile by volume) and small (<10 ml) infarct baseline infarct volumes. Recanalization was assessed on MRA within 24 h post-stroke using the Thrombolysis In Myocardial Infarction (TIMI) (Anon, 1985) recanalization score (M.A.). TIMI scores of 2 and 3 (partial and complete recanalization) were considered evidence of positive recanalization.

2.4. Statistical analysis

Values are reported as mean and standard deviation (SD) unless otherwise noted. Normality was tested using the Kolmogorov–Smirnov tests. The difference between lesion volumes at different time points was investigated using the Mann–Whitney and Kruskal–Wallis rank tests. The relationship between lesion volumes at different time points was investigated using a Spearman rank correlation test. $p < 0.05$ was considered statistically significant.

3. Results

Overall 964 patients were screened from both MONITOR (Simon et al., 2005) and VISION (Coutts et al., 2008; Coutts et al., 2011) studies, and 59 patients were eligible for inclusion in this sub-study. One patient with evidence of acute hemorrhage and two patients with significant motion artifact were excluded, leaving a total of 56 patients included in this analysis. The numbers of scans at each imaging time point were 56 (baseline), 17 (12-hour), 29 (1-day), 56 (7-day), and 56 (>30 day). Patient demographics are shown in Table 1. Post-onset interval for the DWI was 2 ± 2 h (range: 0.5–6 h), and for the follow-up FLAIR imaging at the pre-defined nominal study time points was: 12 h (13 ± 8 h, range: 4–26 h), 1 day (1.1 ± 0.3 day, range: 0.7–1.9 day), 7 days (6.5 ± 2.7 days, range: 3–11 days), and >30 days (57 ± 11 days, range: 22–111 days).

An example of infarct volume evolution at different time points is shown in Fig. 1. Infarct volume at each time point were: 6.45 ± 8.03 ml (baseline), 9.32 ± 9.33 ml (12-hour), 18.81 ± 21.40 ml (1-day), 16.86 ± 23.07 ml (7-day) and 9.51 ± 14.84 ml (>30 day). The measured infarct volumes across all time points for all patients were not normally distributed (Kolmogorov–Smirnov normality tests, $p \leq 0.003$). Fig. 2 shows the median and quartile ranges for infarct volume. The differences in the median values of infarct volumes were significantly different (Kruskal–Wallis test, $p \leq 0.001$). The mean ± SD values of the infarct expansion index by follow-up time were: 1.27 ± 0.97 (12-hour), 2.59 ± 1.80 (1-day), 2.44 ± 1.88 (7-day) and 1.52 ± 1.36(>30 day). Similar to the infarct volumes, the infarct expansion indices were significantly different (Kruskal–Wallis test, $p \leq 0.001$). The distribution of infarct expansion indices including median and quartile ranges is presented in Fig. 3.

Table 1
Patient baseline characteristics.

Characteristics	Value
Mean age years (SD)	68 (12)
Female sex, number (%)	24 (43)
Hypertension, number (%)	30 (54)
Mean glucose level (mmol/l) (SD)	7.2 (2.6)
Diabetes mellitus, number (%)	9 (16)
Right hemisphere (%)	27 (48)
Mean systolic pressure (mm Hg) (SD)	156.2 (28.9)
Mean diastolic pressure (mm Hg) (SD)	82.5 (18.9)
Mean baseline NIHSS (SD)	5 (5)
Thrombolytic treatment, number (%)	12 (21)