Capillary Index Score and Correlation with Outcomes in Acute Ischemic Stroke: a Meta-analysis

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Abstract

Background and Purpose—The capillary index score (CIS) has been recently introduced as a metric for rating the collateral circulation of ischemic stroke patients. Multiple studies in the last five years have evaluated the correlation of good CIS with clinical outcomes and suggested the use of CIS in selecting patients for endovascular treatment. We performed a meta-analysis of these studies comparing CIS with clinical outcomes.

Methods—We conducted a computerized search of three databases from January 2011 to November 2015 for studies related to CIS and outcomes. A CIS = 0 or 1 is considered poor (pCIS) and a CIS = 2 or 3 is considered favorable (fCIS). Using random-effect meta-analysis, we evaluated the relationship of CIS to neurological outcome (modified Rankin scale score ≤ 2), recanalization, and post-treatment hemorrhage. Meta-regression analysis of good neurological outcome was performed for adjusting baseline National Institutes of Health Stroke Scale (NIHSS) between groups.

Results—Six studies totaling 338 patients (212 with fCISs and 126 with pCISs) were included in the analysis. Patients with fCIS had higher likelihood of good neurological outcome [relative risk (RR) = 3.03; confidence interval (CI) = 95%, 2.05–4.47; p < 0.001] and lower risk of post-treatment hemorrhage (RR = 0.38; CI = 95%, 0.19–0.93; p = 0.04) as compared with patients in the pCIS group. When adjusting for baseline NIHSS, patients with fCIS had higher RR of good neurological outcome when compared with those with pCIS (RR = 2.94; CI = 95%, 1.23–7, p < 0.0001). Favorable CIS was not associated with higher rates of recanalization.

Conclusions—Observational evidence suggests that acute ischemic stroke patients with fCIS may have higher rates of good neurological outcomes compared with patients with pCIS, independent of baseline NIHSS. CIS may be used as another tool to select patients for endovascular treatment of acute ischemic stroke.

Introduction

The degree of collateral circulation has been identified as a major factor in determining the outcomes of acute ischemic stroke secondary to large vessel occlusion [1]. Adequate collateral blood flow mitigates infarct growth and post-treatment hemorrhage and increases the likelihood of recanalization and reperfusion [2–7]. Many studies have shown that the presence of good collaterals is associated with good clinical outcome [5,6,8–14].

The capillary index score (CIS) has recently been proposed as a method of rating the collateral circulation of acute ischemic stroke patients [9]. CIS was suggested to improve patient selection for endovascular treatment, and it is thought to be a reliable predictor of patients who will achieve a good clinical outcome following endovascular treatment [8]. Several studies have been published in the last five years for evaluating the usefulness of the CIS and its correlation with clinical outcomes [8–13]. However, the relatively small individual study sizes and the still small number of studies limit the ability of clinicians to determine the practicality of CIS in patient selection or as a predictor of outcomes. Due to these pitfalls, we performed a systematic review and a meta-analysis of studies that evaluated CIS in relation to outcomes in patients undergoing intra-arterial therapy for acute ischemic stroke.
Methods

Literature Search
To identify comparative studies on the CIS and outcomes, an experienced librarian searched the three databases Ovid EMBASE, Ovid MEDLINE and Web of Science for articles from January 2011 to November 2015. The keywords “capillary index score, mechanical thrombectomy, stroke, acute ischemic stroke, collaterals, and outcome” were used for the search. Both published manuscript and abstract presentations were included in the search. After the initial search was complete, the references of the identified articles were assessed to find any other relevant articles.

The initial studies were, then, further evaluated by two authors for inclusion in the meta-analysis. The inclusion criteria were the following: 1) studies properly assigning CISs as described by Al-Ali et al. [9], 2) studies comparing CISs with some relevant clinical outcomes between two separate groups (i.e., favorable CIS and unfavorable CIS), 3) studies reporting separate outcome data for the two groups, and 4) studies with 20 or more patients. Favorable CIS was defined as a CIS of 2 or 3, and unfavorable CIS was defined as a CIS of 0 or 1. Studies were excluded if they: 1) did not stratify outcomes by CIS or 2) had less than 20 patients.

Capillary Index Score
The CIS was initially described by Al-Ali et al. as a method to evaluate the adequacy of collateral flow in the ischemic area [9]. CIS assumes that capillary blush on a cerebral angiogram indicates viable tissue. The CIS is used only in cases of intra-cerebral internal carotid artery or M1 branch of the middle cerebral artery occlusions. To determine the CIS on a digitally subtracted angiogram, the bilateral common carotid arteries and the dominant vertebral artery are injected and assessed through the venous phase for capillary blush. The ischemic area is divided into three equal parts, and each part is given a score of “0” or “1.” A score of “0” indicates no capillary blush, while a score of “1” indicates normal capillary blush. The scores for the three parts are added up to give a CIS range of 0–3. A CIS = 0 or 1 is considered poor (pCIS), and a CIS = 2 or 3 is considered favorable (fCIS). The higher scores indicate that greater ischemic area is potentially viable for recovery following recanalization. An example of how CIS is calculated is shown in Figure 1.

Outcomes
Each study separated the patients into two groups of favorable CIS and poor CIS. Studied outcomes included rates of good neurological outcome, recanalization, and post-recanalization hemorrhage. Good neurological outcome was defined as a modified Rankin scale score (mRS) ≤ 2 at 90 days. Recanalization was defined as thrombolysis in cerebral infarction ≥ 2b or thrombolysis in myocardial infarction ≥ 2. We also extracted data on baseline National Institutes of Health Stroke Scale (NIHSS) scores and time to recanalization when available for each group.

Risk of Bias Assessment and Evaluation of Study Characteristics
Risk of bias assessment was performed using the Newcastle-Ottawa Scale. This is a tool used for assessing the quality of non-randomized studies included in system-
atic reviews and/or meta-analyses. Each study is judged on eight items categorized into three groups: 1) selection of the study groups, 2) comparability of the study groups, and 3) ascertainment of the outcome of interest [15]. Factors examined in our assessment of risk of bias were the following: 1) similar baseline NIHSS between groups, 2) similar time to revascularization between groups, 3) use of angiographic core labs, 4) patient-reported mRS scores at 90 days, and 5) similar revascularization techniques between groups.

Statistics
We extracted a $2 \times 2$ table for each binary outcome from each study. Random-effect meta-analysis was used for pooling across studies [16]. The $I^2$ statistic was used to express the proportion of inconsistency that is not attributable to chance [17]. Meta-analysis results were expressed as relative risk (RR) and 95% of confidence interval (CI). We planned to explore the impact of publication bias by constructing funnel plots and testing their symmetry if a sufficient number of studies (>20) was available. A meta-regression analysis for good neurological outcome was performed for adjusting baseline NIHSS between groups in studies which included such data. Meta-analysis was conducted using Stata (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results
Literature Search
Fifteen articles were found on the initial literature search. Of these articles, eight were excluded (53.3%) after reading the abstract because they did not use the CIS or did not include any clinical outcome data. One additional article was excluded, because only percentages of the patients in each group were given. In total, six studies were included in the meta-analysis: four were published in full text and two were abstract presentations given at conferences. A flow chart that describes the study selection process is shown in Figure 2. Not all of the studies provided data on all outcomes. In addition, data regarding good neurological outcome from [13] were excluded because it was defined as mRS $\leq 3$. The largest study contained 146 patients (106 with fCISs and 40 pCISs), and the smallest study included 26 patients. The studies and the available outcomes from each are summarized in Table 1. In total, 338 patients were included in this study, 212 in the fCIS group and 126 in the pCIS group.

Baseline NIHSS and Time to Recanalization
The baseline NIHSS scores were significantly different between the two groups ($p = 0.003$). The mean baseline NIHSS score in the fCIS group was 17.5 (16.1–18.9) and 19.5 (18.2–20.8) in the pCIS group ($p = 0.003$). The time to recanalization was not statistically different between the two groups with the mean in fCIS group
Outcomes

Favorable CISs were associated with higher RR of good neurological outcome (RR = 3.03; CI = 95%, 2.05–4.47; p < 0.001) compared with pCIS [Figure 3 (forest plot)]. Fifty-nine percent (112 of 191) of patients with fCIS had good neurological outcome compared with 18% (21 of 114) of patients with pCIS. On meta-regression adjusting for baseline NIHSS, patients with fCIS had higher RR of good neurological outcome when compared with those with pCIS (RR = 2.94; CI = 95%, 1.23–7; p < 0.0001).

There was lower risk of post-treatment intra-cerebral hemorrhage within the fCIS group (RR = 0.38; CI = 95%, 0.19–0.93; p = 0.04). Favorable CIS was not associated with higher rates of recanalization (RR = 1.18; CI = 95%, 0.99–1.41; p = 0.06). These data are summarized in Table 2. Forest plots for hemorrhage and recanalization are provided in Figures 4 and 5.

Study Heterogeneity

The I² values were <50% for the three main outcomes: 1) good neurological outcome (I² = 38%), 2) post-treat-
Table 2. Meta-analysis Results: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (fCIS versus pCIS)</th>
<th>95% CI</th>
<th>P Value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Neurological Outcome (mRS ≤ 2)</td>
<td>3.03</td>
<td>2.05–4.47</td>
<td>&lt;0.001</td>
<td>38%</td>
</tr>
<tr>
<td>Post-Treatment Hemorrhage</td>
<td>0.38</td>
<td>0.16–0.93</td>
<td>0.04</td>
<td>0%</td>
</tr>
<tr>
<td>Recanalization</td>
<td>1.18</td>
<td>0.99–1.41</td>
<td>0.06</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 4. Forest plot for post-treatment hemorrhage.

Figure 5. Forest plot for recanalization.
ment hemorrhage ($I^2 = 0\%$), and (3) recanalization ($I^2 = 0\%$). These values indicate relatively low heterogeneity among the studies.

**Discussion**

We conducted a systematic review and meta-analysis of five studies reporting on 338 patients and found that patients with favorable CISs had higher rates of good neurological outcome (mRS ≤ 2) following endovascular therapy for acute ischemic stroke when compared with those with a poor CIS, even when adjusting for baseline NIHSS. Patients with fCIS had significantly lower rates of post-treatment hemorrhage and trended toward higher recanalization rates as well. These findings are important as they suggest that CIS is a potentially useful tool in predicting outcomes following endovascular treatment of acute ischemic stroke.

Proposed applications of the CIS are in patient selection and prognostication. Many of the individual studies and this meta-analysis found fCIS and good neurological outcome to be strongly correlated. The relationship of collateral grade to clinical outcome supports the hypothesis that fCIS can identify viable ischemic tissue that may be amenable to revascularization; however, there is no guarantee that the tissue will recover with or without endovascular intervention. In addition, identifying patients with pCIS can be valuable. Reperfusing patients with pCIS can be harmful because reperfusing nonviable tissue may lead to hemorrhagic transformation and edema, as demonstrated in our study. Our findings reaffirm the importance of collaterals and CIS in predicting clinical outcomes, independent of baseline NIHSS. It is important to point out, however, that fCIS cannot be the sole determinant in patient selection for endovascular therapy. The degree of collateral flow can help predict the likelihood of good outcomes, but the absence of good flow should not prevent endovascular therapy[6]. In patients with pCIS, 18% still recovered with good neurological outcome.

A number of studies have been published examining efficacy of other collateral grading systems in predicting outcomes of endovascular therapy for treatment of acute ischemic stroke. In general, poor collaterals are associated with lower rates of good neurological outcomes and higher rates of hemorrhage, similar to those seen with the CIS [3,18,19]. In a large meta-analysis of 19 studies over the last 15 years that compared collateral grades with outcomes, Leng et al. found that good pre-treatment collateral status almost doubled the rate of good neurological outcome as compared with patients with poor collaterals ($RR = 1.98; CI = 95\%, 1.64–2.38; p < 0.001$) [14]. Of the 19 studies, the majority graded collaterals using DSA imaging, primarily on the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology scale [20]. One potential advantage of the CIS scoring method over traditional DSA-based collateral scoring methods is the fact that the scale is easily quantifiable with high rates of inter-observer agreement [11]. Furthermore, the scale evaluates the functionality of collaterals by assessing capillary perfusion rather than the presence of collaterals alone.

In addition, several studies have used collateral grading methods based on CT angiography and CT perfusion techniques [21–24]. One advantage of CT-based collateral scores is the fact that they rely on non-invasive imaging and can, thus, be used for patient selection prior to conventional angiography. These scores may be more advantageous because they truly evaluate the enhancement and extent of collateral vessels in the ischemic territory. To date, no studies have been performed comparing the accuracy of CTA-based scoring systems and the CIS in predicting good neurological outcome following endovascular therapy.

**Limitations**

This study has several limitations. First, there were a relatively small number of studies included in analysis. This may be due to the relatively short time since the introduction of the CIS. In addition, not all studies had each of the investigated outcomes, further adding to the small size and limiting the power of the meta-analysis. Each of the studies included was retrospective and non-randomized, further limiting certainty in the observed estimates. Baseline NIHSS scores were lower in the fCIS group and likely played a role in the association of the score results and outcome. It is important to point out, however, that in meta-regression of good neurological outcomes adjusting for baseline NIHSS, fCIS was still significantly associated with good neurological outcome. Differences in grading the CIS, quality of angiogram scored, and rater experience among the included studies could not be evaluated. Publication bias was not assessed because our meta-analysis incorporated less than 10 studies. Overall, the quality of the evidence (i.e., confidence in the estimates of effect) is low.

**Conclusion**

Observational evidence suggests that acute ischemic stroke patients with favorable CISs had higher rates of good neurological outcomes, independent of baseline NIHSS. These findings suggest that CIS can be used as
a tool to prognosticate outcomes of endovascular treatment of acute ischemic stroke. It is important to point out that nearly 20% of patients with a pCIS had good neurological outcome following endovascular treatment, thus suggesting that CIS should not be used as the only tool for patient selection at this time.

References

12. Labeyrie PE, et al. The capillary index and aspect scores are strong predictors of patient outcome in the interventional management of ischemic strokes. *Stroke* 2015;46