INTRODUCTION

The aim of ischemic stroke therapy is reperfusion of the ischemic penumbra tissue in order to salvage threatened but potentially viable brain tissues. To improve clinical outcomes of stroke patients, various treatment methods have been developed, with each having its advantages and limitations. Since the MR CLEAN study, the first report showing that int-

Comparison the Perfusion/Diffusion Mismatching Judging From CT-Based and MR-Based Study

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Background

The development of endovascular devices and clinical experience, recanalization rate after intraarterial thrombectomy (IA-Tx) has increased. Recent papers reported that the amount of perfusion/diffusion (P/D)-mismatching in digital analysis from computer tomography perfusion (CTP) image is well correlated well with P/D-mismatching from magnetic resonance image. The purpose of this study is compare the patient clinical outcomes after IA-Tx, judging from CTP based and magnetic resonance imaging (MRI) based study.

Methods

218 patients with anterior circulation large vessel occlusion (LVO) treated by IA-Tx were included in this analysis. In the MRI group (n=80), P/D-mismatching from MRI based image analysis by visual method and in the CTP group (n=138), and recently, P/D-mismatching was decided by automatized computer programmatic analyzed from CTP based image (Syngo.via program).

Results

Favorable outcome (modified Rankin Score: 0–2), mortality, recanalization, and clinically significant hemorrhage was 56.3% (45/80), 6.25% (5/80), 81.3% (65/80) and 25% (20/80) in MRI group and 4.9% (62/138), 8.9%(18/138), 91.3%(126/138) and 40.6% (56/138) in CTP group (p=0.000, 0.235, 0.007 and 0.013). Reperfusion injury (27.5% vs, 15.0%, p=0.018) but favorable outcome was high 55.0% vs. 44.9 %, p=0.00) in the MRI study group.

Conclusion

In our study, patient selection according to the P/D-mismatching from MR-based imaging and CTP-based image was not different in final clinical outcome. Recent IA-Tx, showed high recanalization rate but it also cause high incidence of reperfusion injury.

Keywords: Computer tomography perfusion; Intraarterial thrombectomy; Hemorrhagic complication; Perfusion-diffusion; Recanalization rate; Reperfusion injury

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traarterial thrombectomy (IA-Tx) is more favorable for improve clinical outcomes than intravenous tissue plasminogen activator (IV-tPA) in large vessel occlusion (LVO) patients. Recently, thanks to the development of endovascular devices and clinical experience, the percentage of recanalization rate has increased from about 70–80% to over 95%.

Although successful recanalization rate is increasing, but in some cases, reperfusion treatment can result unfavorable outcomes. In this futile recanalization patients, there is no clinical benefit for a successful recanalization that may sometimes cause an unexpected brain injuries. To avoid the reperfusion injury and to obtain the patient safety and treatment effectiveness of IA-Tx, proper patient selection for IA-Tx is increasingly important.

Many papers have reported that perfusion/diffusion (P/D)-mismatch on brain magnetic resonance imaging (MRI) image might be the best method for selecting IA-Tx patients. Nonetheless, MRI evaluation of acute ischemic patients has several limitations, including a relative long time required to acquire image, high cost, equipment limitations, and patient related reasons. Recent several years, papers have reported that brain computed tomography (CT) image is as informative as P/D-mismatch on magnetic resonance (MR) but clinical application of these CT image instead of MRI image was questionable.

From the three or four years ago, we are facing an additional challenge that we have never experienced before, namely the coronavirus disease 2019 (COVID-19) pandemic. Owing to the additional risk caused by the pandemic, we are unable to evaluate MRI images of stroke patients, especially if the patient shows fever or chest problems on chest X-ray. Serologic diagnostic testing for COVID-19 requires at least 6 hours.

For these several reasons, a CT-perfusion (CTP) with and digitalized computerized program (Syngovia, Siemens Healthcare GmbH, Erlangen, Germany) was used instead of MR-based P/D-mismatching, to select infarction patients for IA-Tx. In this study, although we could not checked CTP and MRI on the same patient, compared clinical outcome between the 80 patient data treated with IA-Tx who was selected by the MR-based image study before the pandemic period and the 138 patient data who was selected by CTP based image after the pandemic season.

**METHODS**

This retrospective, observational study was approved by our Institutional Ethics Committee. The treatment protocol was approved by our Institutional Review Board (approval number: PC17RESI0028). All patients or their representatives provided written consent for treatment.

**Patient characteristics**

From Mar. 2015 to Nov. 2022, a total of 218 patients diagnosed with anterior circulation LVO and treated with IA-Tx were included in this study. In the MRI group, from Mar. 2015 to May 2018, 80 patients underwent CT-angiography (CTA) as an initial image study and checked stroke MRI (Magnetone Vidam, Siemens Medical System, Nucich, Germany) about 1 hours after IV-tPA administration and before the IA-Tx. MRI study was taken. And in CTP group, 63 patients admitted between Jun. 2019 and Nov. 2022 underwent a CTA as an initial image study and decide the IV-tPA administration or not. Than a CTP (Somatom Definition Edge, Siemens Medical Systems, Forchheim, Germany) was checked before the IA-Tx. If the neurologic status (evaluated by NIHSS or motor grade) of the patient was not improved after IV-tPA, the patient was brought to an angiography suite for additional IA-Tx therapy (Fig. 1).

The mean age of patients was 69.8 ± 12.6 years (range, 20 to 98 years, median: 70 years). There were 124 (56.9%) male patients. Eighty (36.7%) patients was MRI group and 138 (63.3%) patients was CTP group. There was no significant difference in a gender (p = 0.795), initial NIHSS score (p = 0.529), or gender (p = 0.499) between the two groups (MRI and CTP groups) (Table 1).

**Fig. 1.** Flow diagram of magnetic resonance based treatment protocol. CT: Computer tomography; IV-tPA: Intravenous tissue plasminogen activator; MRI: Magnetic resonance imaging; GCS: Glasgow Coma scale; EVD: Extraventricular drainage.
ever, analysis for in IV-tPA treated before the IA-Tx, revealed that the IV-tPA administration (42/80 in MRI group vs. 44/138 in CTP group, p = 0.002) faster in CT group and femoral artery puncture time (5.9 hours in MRI group vs. 6.9 hours in CTP group, p = 0.000) was faster in MR group.

Radiologic analysis

Each patient's radiological results were analyzed (visual analysis of MR perfusion-diffusion mismatching) by radiologists after an acute treatment was completed. If radiologists' conclusions regarding a patient's images were not in agreement, another radiologist was consulted. For CTP group, ischemic core and penumbra area were calculated using a Syngo.via program (Siemens Healthcare GmbH, Erlangen, Germany).

All scans were done with 40 cc of nonionic iodinated contrast (Isovue-370, iopamidol, 370 mg iodine/mL; Bracco Diagnostics, Princeton, NJ, USA). In the digitalized automatic program (Syngovia CT Neuro Perfusion VB40), recently defined thresholds for infarcted and hypoperfused tissues (relative cerebral blood flow (rCBF) < 30% and Tmax > 6 s, respectively) were used\(^2,5,8-11,14,16-19\).

Targeted mismatching ratio was defined to be more than 1.8. It was calculated from the ischemic penumbra area divided the ischemic core area. Acute stroke MRI studies have described diffusion weighted image (DWI) and perfusion weighted image (PWI) techniques elsewhere\(^2,20\). A P/D-mismatching profile was defined as a PWI lesion > 180% or more of the DWI lesion\(^21\). Recanalization was measured using the thrombolysis in cerebral infarction (TICI) score. Successful recanalization was defined as TICI grade 2b/3\(^3\).

In patients treated with IA-Tx, a follow-up plain CT image was obtained immediately after IA-Tx. Clinically significant ICH was defined as a hemorrhage identified on the follow-up CT scan associated with a 4 point or greater increase in National Institute of Health Stroke Score (NIHSS) score, consistent with the European Cooperative Acute Stroke Study (ECASS) I & II criteria\(^13,31\). Reperfusion injury was defined as a disastrous outcome in the form of fatal edema or intracranial hemorrhage that concomitantly reversed benefits of re-establishing CBF following mechanical or chemical therapies for acute ischemic stroke\(^10,12\).

### Table 1. Characteristics and clinical outcomes of the 143 patients treated with IA-Tx

<table>
<thead>
<tr>
<th>Patients no.</th>
<th>Magnetic resonance base group</th>
<th>Computer tomography base group</th>
<th>Significance statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (median)</td>
<td>64.2 ± 12.1 (70)</td>
<td>73.0 ± 11.8 (73)</td>
<td>0.999</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>45 (56.3)</td>
<td>79 (57.2)</td>
<td>0.499</td>
</tr>
<tr>
<td>NIHSS score (Median)</td>
<td>13.2 ± 6.3 (12)</td>
<td>12.4 ± 6.8 (13)</td>
<td>0.007</td>
</tr>
<tr>
<td>Occlusion vessel site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA Lt. (%)</td>
<td>19 (33.8)</td>
<td>48 (34.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Rt. (%)</td>
<td>30 (37.5)</td>
<td>54 (39.1)</td>
<td></td>
</tr>
<tr>
<td>ICA Lt. (%)</td>
<td>16 (20.0)</td>
<td>17 (12.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Rt. (%)</td>
<td>15 (18.8)</td>
<td>19 (13.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time to femoral puncture</td>
<td>5.9 ± 2.6 (6.0)</td>
<td>6.8 ± 5.0 (5.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical outcomes (mRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>5</td>
<td>0.000</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>22</td>
<td>0.235</td>
</tr>
<tr>
<td>Favorable (%)</td>
<td>44 (55.0)</td>
<td>62 (44.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>55</td>
<td>0.018</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>6 (Mortality)</td>
<td>5 (6.3)</td>
<td>18 (8.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Recanalization (%)</td>
<td>65 (81.3)</td>
<td>126 (91.3)</td>
<td></td>
</tr>
<tr>
<td>sICH (%)</td>
<td>20 (25.0)</td>
<td>56 (40.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Reperfusion Injury</td>
<td>7 (10.0)</td>
<td>32 (23.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>P/D-mismatching (%)</td>
<td>59/80 (73.8)</td>
<td>116 (84.1)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

NIHSS: National Institute of Health Stroke Score; P/D: Perfusion weighted image/diffusion weighted image; IA-Tx: Intra-arterial thrombolysis; mRS: Modified Rankin Scale; OP: Operation; SD: Standard deviation; sICH: Significant intracerebral hemorrhage.
**Intraarterial thrombectomy**

Angiographic images (Artis Q biplane; Siemens Medical Systems, Nuicht, Germany) were obtained using standard techniques. Usually, the right-side groin was prepped and draped in a sterile fashion. The femoral artery was catheterized with an 8-French sheath and 7-F Terumo guidewire (Terumo Inc., Somerset, NJ, USA) and a 6-French Cello balloon guide catheter (ev3, Irvine, CA, USA) or a Sofia intermediate catheter (MicroVention, Alsio Viejo, CA, USA) in some cases were inserted through the guiding catheter. Multiple runs in multiple views were obtained to identify the site of occlusion. The diseased segment was catheterized highly selectively with a Marksman (ev3, Irvine, CA, USA) and Synchro 2 (Boston Scientific, Natick, MA, USA). Mechanical thrombectomy was performed using a Solitaire FR device (ev3, Irvine, CA, USA), a Trevo 18 microcatheter (Stryker, Kalamazoo, MI, USA), and Penumbra suction devices combining an outer Penumbra catheter and an inner Rebar 18 microcatheter (ev3, Irvine, CA, USA). The stent was usually deployed and kept in place about five minutes. It was then retrieved with aspiration through the balloon guide device. This procedure was repeated until the occlusion site opened. However, in some patients, recanalization efforts failed or the stent device became detached at the occluded site. After IA-Tx procedure, all patients were transferred to the neurosurgical intensive care unit for several days.

**Surgery indications for decompressive craniectomy and postoperative management**

DC indications were the followings: (1) the appearance of massive unilateral brain swelling on computed tomography (CT) scans with correlating clinical deterioration, (2) worsening of Glasgow Coma scale (GCS) score ≤ 8 and/or dilated pupils that were unresponsive to light, (3) midline shift of more than 6 mm, and/or (4) obliteration of cistern structures on CT scans. Patients with primary fatal brainstem failure, indicated by an initial and persisting GCS score of 3 and/or bilaterally fixed and dilated pupils, were excluded from the surgical decompression. After the decompressive surgery, conventional medical managements, including hyperosmotic agents, hyperventilation, and extraventricular drainage (EVD), were initiated if the ventricular pressure exceeded 20 mmHg.

**Variables assessed**

Factors included age, sex, NIHSS score on admission, IV-tPA administration or not, P/D-mismatch on visual analysis on stroke MRI image and digitalized computerized analysis on CTP image, and time from the onset of symptoms to IA-Tx intervention, recanalization rate, complications, and clinical outcomes were analyzed. Clinical results were analyzed according to the MRI based analysis and digital analysis (Syngovia program) in CTP group. A favorable or good outcome was defined as a mRS score of 0 to 2. Complications including postoperative clinical significant ICH, massive brain edema and reperfusion injury were analyzed.

**Statistical analyses**

All data are presented as a mean ± standard deviation and/or a median. A Wilcoxon signed-rank test was used to analyze NIHSS score and mRS. Unpaired t-test and Fisher’s exact test were used to analyze results between groups. Statistical analyses for each outcome were analyzed using SPSS® software version 20 (IBM, Armonk, NY, USA). For all statistical analyses, significance level was defined at p-value ≤ 0.05.

**RESULTS**

**Clinical outcomes according to the MRI group and CTP group**

Patient demographic and clinical results between the MRI group and the CTP group were compared in Table 1. The mean initial neurologic status (evaluated with NIHSS) was 13.2 ± 6.3 (median: 12) for the MRI group and 12.6 ± 6.8 (median: 13) for the CTP group, showing no significant difference between the two groups (p = 0.520) (Table 1).

Favorable outcome (modified Rankin Score: 0–2), mortality, reperfusion injury, and clinically significant hemorrhage was 56.3% (45/80), 6.25% (5/80), 81.3% (65/80) and 25% (20/80) in MRI group and 4.9% (62/138), 8.9% (18/138), 91.3% (126/138) and 40.6% (56/138) in CTP group (p = 0.000, 0.235, 0.007 and 0.013).

Reperfusion injury was 81.3% (65/80) in the MRI study group and 91.3% (126/138) in the CT study group (p = 0.007) (Table 1). Favorable outcome (27.5% in CT group vs. 15.0% in MR group, p = 0.018) but favorable outcome was high 55.0% vs. 44.9%, p = 0.00) in the MRI study group.

**Compare the clinical outcomes according to IV-tPA or not**

Administration of IV-tPA before IA-Tx did not influence patient outcomes or complications (data not shown). The percentages of patients with successful recanalization, favorable outcomes, or those who died or had hemorrhagic complications after receiving IV-tPA was (90.5%, 49.2%, 4.8%, and 31.7%, respectively) did not differ significantly from those in patients who did not receive IV-tPA (86.3%, 50.0%, 6.3%, and 37.5%, p = 0.306, p = 0.530, p = 0.498, and p = 0.295, respectively).
Complications according to the MRI group and CTP group

Compare the MRI group and CTP group showed that clinical significant ICH was identified in 25.0% (20/80) of patients in the MRI study group and in 40.6% (56/138 of patients in the CTP study group (p = 0.004). After the successful recanalization by IA-Tx, reperfusion injury developed in 40.0% (32/80) of patients in the MRI-based group and in 50.9% (32/63) in the CTP-based group (p = 0.013). In this analysis, mortality did not differ significantly between the both groups 6.3% in the CT group vs. 8.9% in the MR group p = 0.235) (Table 1).

DISCUSSION

Reopening of the occluded vessels before critical cell damage occurs is main principal of cerebral ischemic stroke treatment. During the last several decades, various methods to treat stroke have been developed, with each having its treatment successes and limitations1-4,11,13,14,15,26. After the NINDS study, IV-tPA administration within 3 hours from symptom onset without contraindication has become the standard treatment for ischemic stroke patients3. Since the ECASS III study, the critical therapeutic window was extended to up to 4.5 hours after ischemic symptom onset2. IV-tPA therapy has the merit of early beginning of treatment and limitations of poor recanalization rate and various contraindication for administration. And bridging therapy, in which IV-tPA and IA-Tx are combined, has been reported to result in high successful recanalization rate over 80-90% of patients with acceptable safety4,11,13,15,23,27,28.

More recently, recanalization and favorable clinical outcomes after IA-Tx with or without IV-tPA in major LVO have been reported to be better than those of IV-tPA only3,4. But in some instance, even after a successful reperfusion by the IA-Tx, the treatment result is ultimately futile because the patient’s neurologic status shows no improvement12. While in some instance, patient outcomes are favorable although reperfusion treatment is initiated after what would normally be considered the therapeutic window has passed4,15.

The success of recanalization of LVO, is increasing thanks to the development of new thrombolysis devices and greater interventional experience. However, without proper patient selection protocols, reperfusion therapy may cause unexpected complications and lead to worse clinical outcomes12. Brain imaging technique getting more and more important to select patients, fit for the reperfusion therapy. To find the ischemic penumbra on brain image had tried over the last several decades24-26,11,13,15-16.

At the beginning of IV-tPA treatment, non-contrast CT scan was employed as the standard diagnostic image to exclude ICH. Nowadays, advanced dynamic imaging techniques such as CTA, CTP, and acute stroke MRI have become important31,13,16,23,27,28. It is becoming increasingly important to evaluate the viability of ischemic tissues to improve therapeutic results because the physiologic state is unique for each patient5,13,15. Until now, an MRI based P/D-mismatching is thought to be the best approach for proper patient selection. Many studies have assessed the merit and definition of MRI based P/D-mismatching for patient selection in IV-tPA or IA-Tx treatment2,4,6,13,14,12,28. The specified criteria for the target mismatch profile on several diagnostic image technique were summarized on previous studies. These criteria were: 1) ratio between volumes of critically hypoperfused tissue and the ischemic core of 1.8 or more, 2) an absolute difference between the infarction core and the penumbra area of 15 mL or more; 3) ischemic core volume of less than 70 mL; and 4) less than 100 mL of tissue with a severe delay in bolus arrival (T max > 6 s)5,6,1,13,15,17,9,24,26,80.

Quantitative CTP based, P/D-mismatch classification using CBF and Tmax is similar to perfusion-diffusion MRI. The greater accessibility of CTP may facilitate the generalizability of P/D-mismatch based selection in clinical practice and trials3,17-19.

Although P/D-mismatching identified in an MRI study is the best tool for selecting acute ischemic stroke patients, this method has some practical drawbacks. To obtain an MRI image, a quite long extra time is required. If the patient with metallic implants in the body is a contraindication, some patients with neurologic or respiratory problems may find it impossible to tolerate the MRI process long enough to produce a diagnostic image. In addition, it is impossible on MRI based image study to calculate the mismatching amount in a digitalized program9,10,14,16,14. During the COVID-19 pandemic season, MRI studies to evaluate the infarction core or P/D-mismatch are practically problematic for those with suspected COVID-19 infection or febrile patients. Many papers already reported that CTP based computerized digital analysis for patient selection for P/D-mismatching is as effective as MRI based method1,17,19.

From this study, P/D-mismatching patients in visual analysis showed favorable outcome (modified Rankin Score: 0–2) was 55.0% (44/80) in MRI group and 44.9% (62/138) at digitalized computerized analysis in CTP group (p = 0.000).

Recanalization rate, mortality, clinical significant ICH, and reperfusion injury were variables according to patients and managed interventionists not by treatment methods. Many previous studies have reported that IV-tPA administration before IA-Tx does not influence clinical outcomes2,24,26.

Massive brain edema and clinical significant ICH after IV-tPA or
IA-Tx are defined as reperfusion injuries. In some patients, fail to improve clinical results despite evident recanalization. This might occur due to incomplete tissue reperfusion, injury of the neurovascular unit, and/or distal microthrombosis, which has been termed a “no-reflow phenomenon.” On the other end, there is unregulated reperfusion with hemorrhagic transformation. This process occurs due to activation of inflammatory mediators along with an impaired autoregulatory of the brain vasculature. These factors can predispose blood extravasation when the ischemic brain tissue is ultimately reperfused.

Decompressive craniectomy (DC) to treat massive brain edema caused by major infarction patients is regarded as effective treatment option for patient survival. However, in this study, we did not evaluate the clinical significance of DC treatment because surgical intervention was entirely decided by the neurosurgeon who was in charge of each patient, various surgical indication and surgical method were applied.

In order to improve clinical outcomes and lessen the complications in acute stroke patients, identifying the ischemic core and the penumbra area from the brain image is the most important for patient selection. From this study, MRI based mismatching analysis showed similar clinical outcomes as CTP base mismatching patients selection method, Author would like to emphasize that for image analysis P/D-mismatching from MRI and CTP was similar but for improve the clinical outcome after treatment, proper patient selection and gentle manage the IA-Tx devices is important.

Limitations

Several limitations in our study, this study was not randomized control study. Both image study was not taken at same patients. And according to neurosurgeon, IA-Tx technique and decision make is somewhat different. Except for the P/D-mismatching analysis image technique, other treatments applied as same as possible.

CONCLUSION

In order to improve clinical outcomes and lessen the complications in acute stroke patients, identifying the ischemic core and the penumbra area, P/D-mismatching, is the most important for patient selection. From this study, the CT based P/D-mismatching analysis showed same clinical outcomes as the MR base P/D-mismatching analysis, and gently management of the IA-Tx devices is important, avoid to make a complications.
Comparison the Perfusion/Diffusion mismatching


