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Original Article

Symptomatic Intracranial Hemorrhage after Mechanical Thrombectomy – the Difference between Iso-Osmolar and Low-Osmolar Contrast Media

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Objective: Symptomatic intracranial hemorrhage (SICH) after mechanical thrombectomy (MT) is generally considered a critical complication. Hemorrhagic transformation after ischemic stroke has also been associated with contrast media administration. The objective of our study was to evaluate correlations between contrast media type and incidence of SICH after MT.

Methods: Ninety-three consecutive patients (41 men; mean age, 80.2 years; range, 44–98 years) underwent MT reperfusion (expanded thrombolysis in cerebral infarction score, 2a–3) for acute large-vessel occlusion ischemic stroke within 8 h after symptom onset between April 2020 and July 2023 were retrospectively reviewed. Correlations between contrast media type (iso-osmolar or low-osmolar medium) and incidence of SICH were assessed.

Results: Contrast media were iso-osmolar in 60 cases or low-osmolar in 33 cases. The overall incidence of SICH was 5.5%. The frequency of SICH was significantly lower in the iso-osmolar group (1.7%) than in the low-osmolar group (12.1%; P = 0.033).

Conclusion: Iso-osmolar contrast media was associated with a lower incidence of SICH compared with low-osmolar contrast media in patients after MT.

Keywords ▶ symptomatic intracranial hemorrhage, mechanical thrombectomy, iso-osmolar contrast media

Introduction

A meta-analysis of randomized clinical trials has validated the efficacy of mechanical thrombectomy (MT) for acute ischemic stroke, showing the proportion of patients with a modified Rankin Scale (mRS) score of 0–2 at 90 days was higher in the intervention population than in the control population.[1)] However, mortality at 90 days did not differ between populations.[1)] Symptomatic intracranial hemorrhage (SICH) after MT is generally considered a critical complication. Some studies have identified that 90-day mortality was higher in patients with SICH than in patients without SICH.[2–4)]

Several researchers reported contrast media was associated with intracranial hemorrhage (ICH) regarding endovascular treatment. Khatri et al. reported that microcatheter contrast injection at the occlusion site was associated with ICH in the setting of combined IV/IA (intra-venous/intra-arterial) rt-PA (recombinant tissue plasminogen activators).[5)] Moser et al. recently reported that iso-osmolar contrast media (IOCM) was associated with a lower rate of hemorrhagic transformation compared with low-osmolar contrast media (LOCM) in patients with ischemic stroke.[6)]

The objective of the present study was, therefore, to evaluate correlations between contrast media type and incidence of SICH after MT.

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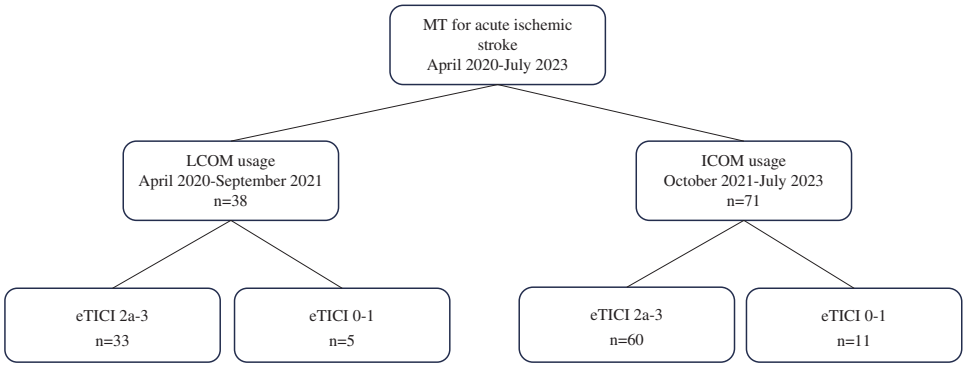

Fig. 1 Flow chart for patients who underwent MT for acute ischemic stroke. eTICI: expanded thrombolysis in cerebral infarction; IOCM: iso-osmolar contrast media; LOCM: low-osmolar contrast media; MT, mechanical thrombectomy

Materials and Methods

In 109 consecutive patients, who underwent MT for acute large-vessel occlusion ischemic stroke (internal carotid artery, middle cerebral artery [MCA] M1 or M2, or basilar artery) within 8 h after symptom onset between April 2020 and July 2023, 93 patients (41 males; mean age, 80.2 years; range, 44–98 years) shown reperfusion after MT (expanded thrombolysis in cerebral infarction [eTICI] 2a–3)[3] and were retrospectively reviewed. Patient flow chart was shown in **Fig. 1**. LOCM were used between April 2020 and September 2021, and ICOM were used between October 2021 and July 2023. Systolic blood pressure (SBP) was controlled to within 100–119 mmHg during the initial 24 h post-MT to prevent SICH.[7]

SICH was defined on the basis of the Heidelberg criteria.[8] SICH was diagnosed if a new intracranial hemorrhage was associated with any of the following conditions: 1) National Institutes of Health Stroke Scale (NIHSS) score increased by ≥4 compared to immediately before worsening; 2) NIHSS score increased by ≥2 in any one category; or 3) deterioration of neurological status leading to intubation, hemicraniectomy, external ventricular drain placement, or other major medical or surgical intervention.

Correlations between contrast media type (iso-osmolar or low-osmolar) and incidence of SICH within 24 h after MT were assessed. The research within our submission has been approved by the ethics institutional review board of Kouseikai Takai Hospital.

Statistical analysis

Continuous variables were analyzed using the Mann–Whitney U test according to the normality of the distribution. Pearson's χ^2 test or Fisher's exact test was used to compare SICH between iso- or low-osmolar groups in univariate analyses.

Results

The contrast medium was iso-osmolar in 60 cases and low-osmolar in 33 cases. The baseline characteristics are summarized in **Table 1**.

The overall incidence of SICH (**Fig. 2**) was 5.5% (5/93). The 90-day mortality rate with SICH was 80% (4/5), and another case developed moderately severe disability (mRS 4) by 90 days after MT. The rate of SICH was significantly lower in the iso-osmolar group (1.7%, 1 of 60 patients) than in the low-osmolar group (12.1%, 4 of 33 patients; P = 0.033).

The 90-day mortality rate was higher in patients with SICH (80.0%, 4/5) than in patients without SICH (14.0%, 12/88; P <0.001) (**Table 2**).

Discussion

In a meta-analysis of randomized clinical trials showing the efficacy of MT for acute ischemic stroke, the rate of successful reperfusion (TICI 2b or 3) after MT was 70.5%, and the proportion of patients with mRS score 0–2 at 90 days was higher in the intervention population (46.0%) than in the control population (26.5%; P <0.0001).[1] Although Goyal et al. reported no significant differences between groups were evident for mortality at 90 days (15.3% in the intervention population vs. 18.3% in the control population), mortality rates at 90 days after MT remained high (15.3%–26.3%).[1–3] Thus, it remains important to understand which factors influence mortality despite successful MT.

SICH after MT reportedly occurred in 4.4%–16.0% of patients.[1,2] SICH following MT seems to be associated

Table 1 Baseline characteristics

	IOCM (n = 60)	LOCM (n = 33)	P value
Age, mean (SD), years	79.1 (11.6)	82.3 (9.2)	0.29
Male sex, n (%)	28 (46.7)	13 (39.4)	0.50
Diabetes mellitus, n (%)	14 (23.3)	9 (27.3)	0.67
Hypertension, n (%)	45 (75.0)	22 (66.7)	0.39
Hypercholesterolemia, n (%)	24 (40.0)	7 (21.2)	0.066
Smoking, n (%)	28 (46.7)	11 (33.3)	0.21
AF, n (%)	36 (60.0)	26 (78.8)	0.066
Antiplatelet agents pretreatment	12	5	0.56
Anticoagulant pretreatment	20	12	0.77
Location of intracranial artery occlusion			
ICA	12	11	0.15
M1	29	12	0.27
M2	17	7	0.45
BA	2	3	0.24
Contrast media volume, Mean (SD), ml	124.1 (60.7)	127.5 (45.8)	0.25
Onset to recanalization, mean (SD), minutes	356.7 (125.5)	359.6 (113.2)	0.91
Stent retriever	49	29	0.44
ADAPT only	11	4	
Passes of retriever >3	10	6	0.85
NIHSS on admission ≥17, n (%)	41 (68.3)	24 (72.7)	0.66
NIHSS after MT (24 ± 6 h) ≥11, n (%)	20 (33.3)	15 (45.5)	0.25
mRS score 0–2 at 90 days, n (%)	20 (33.3)	11 (33.3)	1.00
Mortality at 90 days, n (%)	8 (13.3)	8 (24.2)	0.18

ADAPT: a direct aspiration first pass technique; AF: atrial fibrillation; BA: basilar artery; ICA: internal carotid artery; IOCM: iso-osmolar contrast media; LOCM: low-osmolar contrast media; mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale

with mortality. Hao et al. reported that the 90-day mortality rate was higher in patients with SICH (65.3%, 66/101) than those without SICH (18.8%, 100/531).[2] Efforts should, therefore, be made to minimize the risk of SICH to improve the mortality rate after MT. In the present study, the overall SICH rate was 5.5% and no marked difference was evident compared to previous studies. However, in our study, the rate of SICH in the iso-osmolar group was only 1.7%. Therefore, IOCMs like iodixanol should thus be considered in the treatment of patients with MT for ischemic stroke to reduce mortality after MT.

Matusevicius et al. reported an SBP interval ≥160 mmHg was associated with less functional independence (OR: 0.28, 95%CI: 0.15–0.53) and greater frequency of SICH (OR: 6.82, 95%CI: 1.53–38.09) compared with the reference range of 100–119 mmHg among 2920 patients with successful recanalization after MT.[7] So we controlled SBP to within 100–119 mmHg after the procedure. However, SICH still occurred in some cases. Blood pressure control alone thus may not be enough to prevent SICH. Mazighi et al. reported that an intensive SBP target of 100–129 mmHg after successful MT did not reduce radiographic intraparenchymal hemorrhage rates at 24–36 h as compared to a standard-care SBP target of 130–185 mmHg.[9]

Moser et al. undertook a large, real-world analysis, finding an overall risk reduction in hemorrhagic transformation among patients undergoing MT who received IOCM compared with those who received LOCM, with an absolute risk reduction of 1.4% (P = 0.032).[6] Our study also showed similar results to this study. Although this study was a large number and seemed to be more reliable than our study, these data seemed to include any hemorrhagic transformation, which meant not only symptomatic hemorrhagic but also asymptomatic. In addition, this study data were obtained from the Premier Healthcare Database and hence the procedural details were not shown. In view of clinical daily practice, SICH is much more important than asymptomatic ICH. On the other hand, our analysis demonstrated a significant reduction in the risk of SICH with IOCM use compared to LOCM use among patients presenting with ischemic stroke. So our data seem to be more meaningful.

Khatri et al. reported that among the subset of patients with microcatheter contrast injections (MCI), the rate of any ICH was 58% (57/98).[5] More MCIs were seen in the ICH group (median, 2) than in the non-ICH group (median, 1; P = 0.04), so MCIs may risk intracranial hemorrhage in the setting of combined IV/IA rt-PA therapy, possibly due

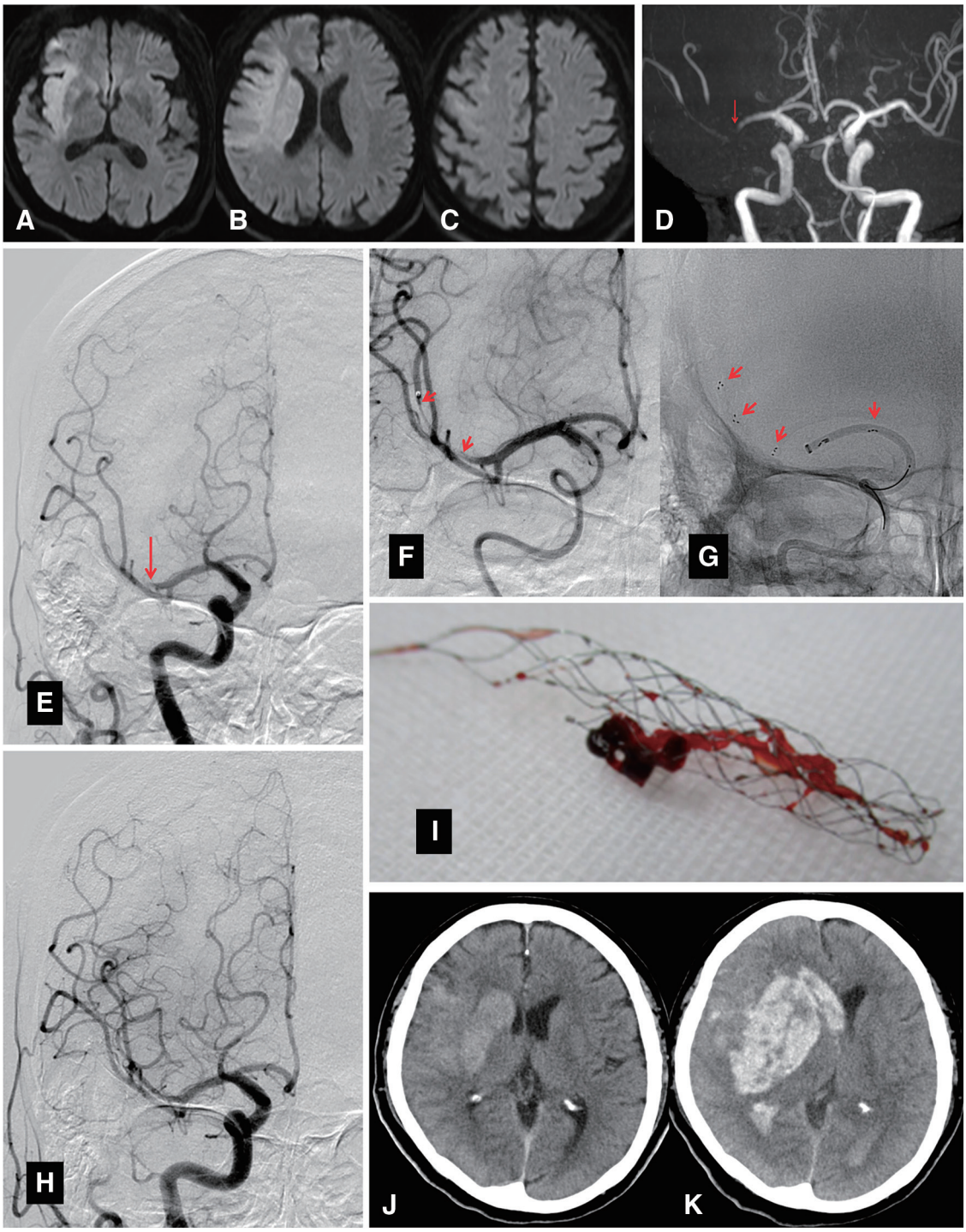

Fig. 2 A 71-year-old female presented to our hospital with a 5-h history of left-sided weakness. The NIHSS score at the time of admission was 6. (**A, B,** and **C**) MRI diffusion imaging before treatment shows mild hyperintensity area suspected acute ischemic lesions in the right frontal lobe and insular cortex. (**D**) MRA shows the M2 occlusion of the right MCA (arrow). She underwent stent retriever thrombectomy combined with aspiration catheter therapy following admission. (**E**) Anteroposterior DSA image before treatment reveals the M2 anterior trunk occlusion of the right MCA (arrow). (**F**) DSA using a simultaneous injection of contrast media (LOCM) from the microcatheter and from the guiding catheter shows a thrombus in the M2 anterior trunk (small arrows). (**G**) A 4 × 40 mm Solitaire stent is placed into the M2 anterior trunk for MT (small arrows). (**H**) Final anteroposterior DSA image shows complete recanalization (eTICI 3) of the right MCA. (**I**) The Solitaire stent is covered with fresh clots. (**J**) Head CT at 1 h after MT shows relative high density in the right frontal lobe and right lenticular nucleus, indicating contrast staining. However, at 6 h after MT, she had loss of consciousness and the NIHSS score at the time was 10 (increased by 4 compared to immediately before worsening). (**K**) Head CT at 6 h after MT shows large hemorrhagic lesions in the right cerebral hemisphere with a significant mass effect. An emergent surgical decompression was performed but the patient's level of consciousness did not improve (mRS 4). eTICI: expanded thrombolysis in cerebral infarction; LOCM: low-osmolar contrast media; MCA: middle cerebral artery; mRS: modified Rankin Scale; MT: mechanical thrombectomy;.NIHSS: National Institutes of Health Stroke Scale

Table 2 Characteristics of patients with and without SICH

	With SICH (n = 5)	Without SICH (n = 88)	P value
Age, mean (SD), y	79.4 (8.7)	80.2 (11.0)	0.45
Male sex, n (%)	2 (40.0)	39 (44.3)	0.85
Diabetes mellitus, n (%)	3 (60.0)	20 (22.7)	0.060
Hypertension, n (%)	3 (60.0)	64 (72.7)	0.54
Hypercholesterolaemia, n (%)	1 (20.0)	30 (34.1)	0.52
Smoking, n (%)	3 (60.0)	48 (54.5)	0.81
AF, n (%)	5 (100)	57 (64.7)	0.10
Antiplatelet agents pretreatment	2	15	0.20
Anticoagulant pretreatment	4	28	0.085
Location of intracranial artery occlusion			
ICA	1	22	0.80
M1	1	40	0.26
M2	3	21	0.072
BA	0	5	0.58
Cause of stroke			
Cardioembolic, n (%)	5 (100)	63 (71.6)	0.16
Atherothrombotic, n (%)	0 (0)	25 (28.4)	
Contrast media			
IOCM, n (%)	1 (20.0)	59 (67.0)	0.033*
LOCM, n (%)	4 (80.0)	29 (33.0)	
Onset to recanalization, mean (SD), minutes	398.4 (113.5)	355.4 (121.2)	0.44
Stent retriever usage and microcatheter contrast injections	4	74	0.81
ADAPT only	1	14	
Passes of retriever >3	1	15	0.86
NIHSS on admission ≥17, n (%)	4 (80.0)	61 (69.3)	0.61
NIHSS after MT (24 ± 6 hours) ≥11, n (%)	4 (80.0)	30 (34.1)	0.038*
mRS score 0–2 at 90 days, n (%)	0 (0)	31 (35.2)	0.10
Mortality at 90 days, n (%)	4 (80.0)	12 (13.6)	0.0001*

ADAPT: a direct aspiration first pass technique; AF: atrial fibrillation; BA: basilar artery; ICA: internal carotid artery; IOCM: iso-osmolar contrast media; LOCM: low-osmolar contrast media; mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institute of Health Stroke Scale; SICH: symptomatic intracranial hemorrhage

to contrast. However in our clinical study, there was no significant differences of microcatheter contrast injections between with the SICH group and without the SICH group; therefore, other factor must be associated with ICH.

The other factor seemed to be the osmolarity of contrast media. The reason why the osmolarity of contrast media was associated with ICH was already reported by animal studies. Morales et al. showed a statistically significant reduction in cortical intracranial hemorrhage with the IOCM iodixanol in comparison with the low-osmolar LOCM iopamidol using reperfusion rat model.[10] In this study, a subsequent MCA occlusion/reperfusion model confirmed their previous results and hypothesized that the presence of HT may represent a direct/indirect effect of radiographic CM in the brain parenchyma, with less impact of IOCM iodixanol compared with LOCM iopamidol.[11] They speculated IOCM might be due to its larger molecular size or reduced hydrodynamic effects of its more viscous macromolecular properties, leading to less leakage across the blood–brain barrier. Also, the osmolality of IOCM is less than 300 mOsm/kg H_2O and almost the same plasma osmolality. Therefore, neurotoxicity seems to be lower in ICOM than in LOCM.[10] In our clinical study, the rate of SICH was significantly lower (1.7%) in IOCM iodixanol use. So, in the human being, intra-arterial infusion of IOCM may reduce cortical intracranial hemorrhage areas in comparison with LOCM.

Some limitations of the present study must be addressed when interpreting the results. The study used a retrospective design and included a relatively small number of cases. A large number of prospective studies to investigate the benefit of IOCM for patients undergoing MT are needed.

Conclusion

Iso-osmolar contrast media was associated with a lower incidence of SICH compared with low-osmolar contrast

media in patients after MT. Therefore, iso-osmolar contrast media should be used to prevent SICH after MT.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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