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Efficacy and Safety of Intra-arterial Thrombolysis in Central Retinal Artery Occlusion

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Abstract

Purpose: To investigate the efficacy and safety of intra-arterial thrombolysis (IAT) for acute central retinal artery occlusion (CRAO).

Methods: Records from 101 CRAO patients treated with either IAT (n = 57) or standard treatment (ST, n = 44) were retrospectively reviewed. ST consisted of ocular massage and intraocular pressure-lowering agents. Using fundoscopic and angiographic findings, CRAO was categorized as incomplete (diminished visual acuity [VA] with slight retinal edema, slight cherry-red spot), subtotal (severe VA reduction, cherry-red spot, distinct retinal edema), or total (massive edema, occluded perimacular arterioles, additional choroidal blood flow interruption). One-month and final best-corrected VA (BCVA) were compared between the IAT and ST groups. Early (≤3 days) and final (1 month) reperfusion (improvement of retinal perfusion) rates were compared between groups. Subgroup analyses were performed according to CRAO stage.

Results: Overall VA did not significantly differ between groups, but early reperfusion was greater in the IAT group (74.1% vs. 42.9%, P = 0.005). In incomplete CRAO, the IAT group exhibited greater visual improvement after 1 month (1.08 ± 0.21 vs. 0.23 ± 0.26 logMAR, P <0.001) and at the final visit (1.08 ± 0.53 vs. 0.08 ± 0.57 logMAR, P <0.001). However, in subtotal and total CRAO, no significant differences in visual outcomes were observed between groups. IAT resulted in clinically insignificant cerebral infarcts, detectable on brain imaging, in 8% of patients. Hemorrhagic transformation was not noted.

Conclusions: The IAT treatment may provide early restoration of retinal perfusion and offer functional benefits in the management of incomplete CRAO.

INTRODUCTION

Central retinal artery occlusion (CRAO) is an ocular vascular occlusive disorder that causes inner retinal ischemia. Visual prognosis in patients with CRAO is poor, as 92% have permanent visual loss, with a final visual acuity of counting fingers or less, and only up to 8% of patients experience meaningful vision recovery.[1-7] The stages of CRAO are as follows[8, 9]: incomplete CRAO is characterized by diminished visual acuity (but no complete visual loss), slight retinal edema with a slight cherry-red spot on the macula, and delayed (but not completely interrupted) blood flow on fluorescein angiography (FA). Subtotal CRAO results in a severe reduction in visual acuity, distinct edema of the central retina with a cherry-red spot on the macula, and a distinct delay in arterial blood flow. Total CRAO is distinguished from the aforementioned stages by massive retinal edema, without a cherry-red spot, a lack of blood flow in the perimacular arterioles, and an additional blood flow interruption of the choroid. Schmidt and Schumacher[9] reported that of 46 patients with CRAO, 26 (56.5%) had subtotal occlusion, 10 (21.7%) had incomplete occlusion, and 10 patients (21.7%) had total occlusion. In another report, 21.9%, 73.0%, and 5.1% of patients with CRAO were classified as incomplete, subtotal, and total CRAO, respectively.[8]

Standard treatment modalities for CRAO include ocular massage, anterior chamber paracentesis, intraocular pressure (IOP)-lowering agents (e.g., mannitol, acetazolamide, topical agents), hyperbaric oxygen, anti-coagulants, and hemodilution.[5-7, 10-24] Thrombolysis has also been used, both intravenously and intra-arterially, for the treatment of CRAO.[1, 25-34] A placebo-controlled, randomized trial by Chen et al.[25] showed that only 2 of 8 patients treated with an intravenous tissue-type plasminogen

activator had an improvement in visual acuity of 3 or more lines. Recently, the European Assessment Group for Lysis in the Eye (EAGLE) trial, a prospective, randomized, multicenter study,[30] compared the effect of intra-arterial thrombolysis (IAT) with that of standard CRAO treatments. This trial showed that the final (1 month) visual outcome was not different between the IAT and standard treatment groups, although IAT caused higher rates of treatment-related adverse reactions.

However, we believe it is unreasonable to disregard IAT as a treatment modality for all cases with CRAO based on the EAGLE trial alone. Although Schmidt and Schumacher[9] reported different IAT efficacies for different CRAO stages, the authors overlooked the heterogeneous nature of CRAO and did not perform a detailed CRAO stage subgroup analysis. Furthermore, the primary outcome was evaluated 1 month after IAT and compared between the 2 treatment groups. Therefore, a comparison of the long-term procedural results could not be obtained from this randomized, prospective study. In addition, anatomic outcome, such as central retinal artery reperfusion, was not evaluated, although central retinal artery reperfusion may be a potential benefit of the intervention.

In the present study, we compared visual and anatomic outcomes between IAT and standard treatment in a relatively large number of patients with CRAO. Additionally, we performed CRAO stage subgroup analyses. Furthermore, we investigated factors associated with IAT treatment outcome and reviewed baseline brain magnetic resonance images (MRI) and those obtained after IAT to evaluate adverse events associated with IAT in depth.

METHODS

Patients

The institutional review board of Seoul National University Bundang Hospital approved this retrospective study, and the study adhered to the tenets of the Declaration of Helsinki. A review of the medical records of consecutive patients diagnosed with acute non-arteritic CRAO from January 2003 through December 2012 at Seoul National University Bundang Hospital was performed. Patients with an initial significant visual disturbance (≤20/63 Snellen visual acuity) and a follow-up period ≥1 month were included.

Eligibility Criteria and Treatment

A CRAO was diagnosed with fluorescein angiography (FA) and fundoscopy in all patients. Patients meeting the eligibility criteria for thrombolysis (Table 1) at initial presentation were considered for IAT. The eligibility criteria of IAT were set as symptom duration <24 hours for subtotal and total CRAO and <7 days for incomplete CRAO. Systemic conditions restricting thrombolysis, including uncontrolled hypertension, coagulation disorders, and anti-thrombotic treatments, excluded patients from receiving IAT. Cases with combined ocular pathologies that might influence visual outcome or other ocular ischemic disease, such as ocular ischemic syndrome, central retinal vein occlusion, and proliferative diabetic retinopathy, were also excluded. Iatrogenic cases of CRAO were also excluded.

The standard treatment group (ST group) included patients who were eligible for IAT but refused the treatment and those who met the eligibility criteria for IAT but visited

the hospital before IAT initiation at our hospital in May 2008. These patients were treated with ocular massage (repeated manual compression for 10-15 s followed by sudden release using a 3-mirror contact lens for 3-5 min) and IOP-lowering agents (topical timolol 0.5%, oral acetazolamide 500 mg).

After an ophthalmologist provided a detailed procedure description and discussed potential complications, IAT was performed, along with cerebral angiography using a biplane angiographic unit (IntegrisAllura; Philips Medical Systems, Eindhoven, Netherlands). The microcatheter (Excelsior SL-10; Stryker Neurovascular, Fremont, CA) was placed in the proximal segment of the ophthalmic artery, and up to 500,000 units of urokinase (Green Cross pharmacy, Yongin, Korea) were slowly injected by hand. During the IAT procedure, an ophthalmologist checked visual acuity and performed fundoscopic examination to evaluate retinal changes following each 100,000-unit injection of urokinase until visual improvement was noticed. If visual improvement was not noted, up to 500,000 units of the thrombolytic was infused, provided the patient had no bleeding risk.

Examinations

We obtained data pertaining to age, gender, and time from symptom onset to treatment. All measurements of best-corrected visual acuity (BCVA) were obtained using a standardized Snellen chart. Snellen visual acuity measurements were converted into the logarithmic minimum angle of resolution (logMAR) equivalent for statistical analysis. The numeric scores for profound low vision, namely, counting fingers or worse, were substituted for logMAR values, as suggested by Lange et al.[35] The amount of

visual improvement at 1 month and at the final visit was calculated by the change in BCVA from baseline. A clinically significant visual improvement was defined as a visual improvement ≥0.3 logMAR.

To quantify the degree of circulatory disturbance in each case of CRAO, the arm-to-retina time until fluorescein appearance[36] and arteriovenous passage time[37] were evaluated for pre-treatment FA images, obtained at the time of CRAO diagnosis. The central retinal artery was considered to be reperfused if follow-up FA images showed reduced arm-to-retina time and arteriovenous passage time. Early reperfusion was assessed using FA images obtained within 3 days of treatment, and final reperfusion was evaluated 1 month after the treatment.

In both the IAT and ST groups, adverse reactions were identified by clinical examinations and from patient symptoms. Sixty-five patients, including 35 in the IAT group and 30 in the ST group, underwent brain MRI at baseline. Thirty-one patients in the IAT group underwent brain MRI after IAT. In 25 patients from the IAT group, diffusion-weighted MRI images obtained before and after IAT were compared to detect new ischemic lesions following IAT. Hemorrhagic or ischemic lesions were confirmed by the consensus from one trained neuroradiologist and 1 trained neurologist.

Statistical Analyses

We compared the final visual and anatomic outcome (reperfusion status) between the IAT and ST groups. After categorizing CRAO into incomplete, subtotal, and total CRAO, as suggested by Schmidt et al.,[8] we analyzed treatment outcomes between the IAT and ST groups. For comparison, the Mann–Whitney U test or Student's *t* test,

depending on normality (determined by the Shapiro-Wilk test), was used to compare means of continuous variables. Dichotomous data were analyzed using the chi-square test or Fisher's exact test.

We also investigated predictive factors for the visual outcome. Multiple regression analyses were performed to identify factors associated with 1-month or final BCVA by using the clinical parameters. Descriptive statistics were performed on baseline cerebral pathologies and adverse reactions following IAT. Commercial software was used for all statistical analyses (SPSS ver. 17.0 for Windows; SPSS, Inc., Chicago, IL). Statistical significance was assigned at $P < 0.05$.

RESULTS

Clinical Characteristics of Included Patients

Out of 127 consecutive acute non-arteritic CRAO patients evaluated during the study period, 101 CRAO patients, (26 [26%] incomplete, 48 [48%] subtotal, 27 [27%] total) met the inclusion criteria (Figure 1). The IAT and ST groups included 57 (13 incomplete, 28 subtotal, 16 total) and 44 (13 incomplete, 20 subtotal, and 11 total) CRAO patients, respectively. The ST group included 33 patients who refused IAT because of safety concerns and 11 patients who visited our hospital before May 2008, the time IAT became available to our acute CRAO patients. These 11 patients were all treated with ocular massage and IOP-lowering agents. Representative cases with CRAO are shown in Figure 2. Significant differences were not found between the IAT (n = 57) and ST (n = 44) groups in the demographic data (Table 2), except time between symptom onset and treatment in the subtotal (16.4 ± 11.2 hours in the IAT group vs.

40.5 ± 30.3 hours in the ST group) and total CRAO subgroups (11.2 ± 6.4 hours in the IAT group vs. 33.0 ± 25.5 hours in the ST group).

Visual Outcome

The mean BCVAs at the initial visit, 1 month after treatment, and final visit are shown in Figure 3. Overall, initial, 1-month, and final BCVAs were not significantly different between the IAT and ST groups (Table 3). Among the patients with subtotal and total CRAO (Table 4), all BCVAs were not significantly different between the two groups. However, subgroup analyses among those with incomplete CRAO revealed significant differences in final BCVA between the groups (1.57 ± 0.73 in the ST group vs.0.83 ± 0.61 in the IAT group, P = 0.020).

Among all the patients, the amount of visual improvement at 1 month (0.13 ± 0.46 [IAT group] vs. 0.05 ± 0.44 logMAR [ST group], P = 0.519) and at the final visit (0.31 ± 0.63 vs. 0.08 ± 0.51, P = 0.062) were not significantly different between the IAT and ST groups. There were no significant differences in visual improvement at 1-month or the final visit between the 2 groups in subgroup comparisons among patients with subtotal or total CRAO (Table 4). However, statistically significant differences were noted in the comparisons between groups of visual improvement at 1-month and at the final visit among patients with incomplete CRAO (both P <0.001).

The percentages of eyes with a BCVA equal to or better than 20/200 and those with a clinically significant visual improvement (≥0.3 logMAR) in the IAT and ST groups are presented in Figures 4A and 4B, respectively. Among all the included patients, percentages were not significantly different between the 2 groups at 1 month after

treatment (P = 0.108 and 0.639, respectively). However, at the final visit, the percentage of eyes with a BCVA equal to or better than 20/200 was significantly greater in the IAT group than in the ST group (19.3% vs.4.5%, respectively, P = 0.026), whereas the percentage of eyes with a clinically significant visual improvement was not significantly different between the 2 groups (42.1% vs. 25%, respectively, P = 0.056). The percentage of eyes with a BCVA equal to or better than 20/200 and that had a clinically significant visual improvement at the final visit were significantly greater in patients with incomplete CRAO treated with IAT than in standardly treated eyes (P = 0.008 and 0.002, respectively). In contrast, the same comparisons among the patients with subtotal or total CRAO revealed no significant inter-group differences at 1 month or at the final visit.

Anatomic Outcome

The early reperfusion rate, as evaluated by FA, was significantly greater in the IAT group than in the ST group (40 of 54 [74.1%] vs.12 of 28 [42.9%], respectively, P = 0.005), whereas the final reperfusion rate was not significantly different (45 of 51 [88.2%] vs. 25 of 31 [80.6%], respectively, P = 0.346). Subgroup analyses revealed significant differences in early reperfusion rates between the IAT and ST groups in incomplete CRAO (100% vs. 55.6%, P = 0.026), as presented in Table 4.

Factors Associated with Visual Outcome

Among the clinical factors examined (e.g., age, sex, CRAO stage, CRAO treatment, initial BCVA, time between symptom and treatment, follow-up period, arm-to-retina time, and arteriovenous passage time), CRAO stage was the only factor

significantly associated with 1-month BCVA (P <0.001, multiple regression analysis). Initial BCVA (P = 0.038) and CRAO stage (P < 0.001) were significantly associated with final BCVA.

Adverse Reactions

Table 5 shows the neurological and non-neurological adverse reactions associated with IAT, as identified by clinical and laboratory examinations and brain MRI. After IAT, we observed cases of hematoma at the vessel puncture site (n = 2 [3.5%]), increased IOP (n = 2 [3.5%]), hemianopsia (n = 1 [1.8%]), headache (n = 1 [1.8%]), tinnitus (n = 1 [1.8%]), and hyperesthesia (n = 1 [1.8%]) in the IAT group (Table 5).

Brain MRI provided detailed information regarding baseline cerebral pathology and adverse reactions following IAT. Eight of 65 (12.3%) patients with CRAO had concurrent acute or old ischemic lesions, which were detected in baseline MRI images. In the IAT group, post-IAT MRI images showed that 8 of 31 (25.8%) patients had acute infarctions. Diffusion-weighted images picked up new ischemic lesions, occurring after the IAT, in 2 of 25 (8%) patients in the IAT group. Among 8 patients showing acute infarctions on post-IAT brain MRI, seven cases were asymptomatic and clinically insignificant. Neurologic examinations did not reveal any sign suggestive of cerebral infarct, and the infarcted lesions in MR images were small. However, 1 patient exhibited hemianopsia due to right occipital lobe infarct with posterotemporal branch occlusion of right middle cerebral artery, followed by immediately mechanical thrombolysis for recanalization that completely recovered within 7 days. No case presented with intracranial hemorrhage or transient ischemic attack following IAT.

After a thorough stroke risk factor workup, including assessment of potential cardioembolic stroke sources, we treated the patient with embolic infarction following IAT with an antiplatelet agent and a cholesterol-lowering medication (statin) for the secondary prevention of stroke. Post-IAT headache resolved after oral non-steroidal anti-inflammatory drug therapy (NSAID) within 1 or 2 days and both the tinnitus and the hyperesthesia only lasted for a few hours and resolved without treatment. Hematomas occurring at the vessel puncture site were not large in our patients and hemostasis was obtained with bed rest and by applying manual compression for 10-20 minutes. Increased intraocular pressure due to neovascular glaucoma required topical IOP-lowering medications and, eventually, valve implant surgery for uncontrolled IOP.

DISCUSSION

This study suggests that IAT may be beneficial for visual recovery in eyes with incomplete CRAO. Although retinal artery reperfusion occurred more frequently in the IAT group among patients with CRAO, patients with subtotal or total CRAO in the IAT group showed comparable visual improvement to those in the ST group. Although the randomized EAGLE trial did not show that IAT is superior to standard treatment, our results suggest that IAT may be beneficial for visual recovery in select cases of CRAO, and that it may be a viable treatment option for these cases. However, in 8% of patients, IAT resulted in a new cerebral infarct that was clinically insignificant, but was detected by comparing brain MRI images before and after IAT. Therefore, the risk of an associated infarct following IAT should be carefully considered when deciding to perform the treatment.

Previously, Schmidt et al. suggested dividing the 3 CRAO stages on the basis of clinical, fundoscopic, and angiographic findings.[8, 9] Their reported subgroup percentages were comparable to ours (26, 48, and 27% for incomplete, subtotal, and total CRAO, respectively). Schmidt and Schumacher[9] reported different IAT efficacies according to the stage of CRAO. They suggested that IAT has a beneficial effect in patients with incomplete CRAO. However, their study did not include a control group, which is essential for providing evidence for IAT use in CRAO. By comparing both functional and anatomical outcomes between the IAT and ST groups in patients with CRAO, our study showed that early reperfusion rates were significantly greater in the IAT group than in the ST group, indicating that IAT has a beneficial effect on reperfusion. The anatomic outcomes might be associated with visual outcome, as the temporal changes in BCVA showed different patterns from 1 month after treatment to the final visit between the IAT and ST groups (further improved and deteriorated BCVA, respectively).

The clinical efficacy of IAT for CRAO has been reported in several retrospective studies and meta-analyses.[26-29, 31, 32, 34] However, the treatment outcomes vary greatly from study to study. Our findings, with regard to visual outcomes, differed from those reported in the EAGLE study. More specifically, the BCVA changes at 1 month in the IAT and ST groups were different between the EAGLE study (0.45 and 0.44 logMAR, respectively) and our study (0.13 and 0.05 logMAR, respectively). The discrepancies in the types of treatment performed for the standard treatment group (6 modalities in the EAGLE trial vs. 3 modalities in our study), the time from onset to treatment (longer in our study), and materials used for thrombolysis may have resulted in the discrepancy in

BCVA changes between previous studies and ours. However, the EAGLE study and ours commonly showed that overall visual outcome was similar between the IAT and ST groups. Our study also suggests that IAT may be beneficial when used for incomplete CRAO.

Retinal survival time after CRAO was reported to be as long as 97–100 min, with irreversible retinal damage occurring beyond 105 min in animal experiments.[35] However, the extreme retinal clamping used in those experimental setting does not reflect the actual clinical condition of CRAO in humans. For incomplete CRAO, the retinal tolerance time may be prolonged and retinal ischemic injury can be reversible after retinal reperfusion by IAT. For instance, 84.6% of patients with incomplete CRAO in the IAT group showed a clinically significant visual improvement at the final visit, while only 14.3% of patients with subtotal CRAO and none with total CRAO had a clinically significant visual improvement after IAT. However, if patients with incomplete CRAO are not treated by IAT and early reperfusion is not obtained, as was the case in the ST group, retinal ischemic injury may lead to permanent visual loss even if reperfusion is spontaneously obtained without invasive procedures in more delayed fashion than in the IAT group. To support this hypothesis, the retinal tolerance time in incomplete CRAO should be investigated in future studies. Regarding the tolerance time, 1 patient with incomplete CRAO showed a clinically significant visual improvement after IAT, which was performed 172 hours after initial symptom onset. On the basis of this finding, our eligibility criterion for IAT was set at a ≤7-day interval from symptom onset to treatment in cases of incomplete CRAO.

The major complication related to IAT was cerebral infarct, and the minor

complications included headache, dizziness, and increased IOP. The EAGLE study reported IAT-related major complications (cerebral and cerebellar hemorrhage) in 2 of 44 patients (4.5%). One of the main reasons for the early termination of the EAGLE trial was the higher rate of complications in the IAT group, including 2 cases with cerebral or cerebellar hemorrhage. The main safety concern after thrombolytic therapy is hemorrhagic transformation of the infarct.[38] Therefore, with regard to evaluating the safety of IAT, baseline brain imaging, which was not obtained in the EAGLE trial or in the study by Chen et al., would be valuable for detecting cerebral infarct before thrombolysis and for assessing the risk of hemorrhage and infarction associated with IAT.[39] In our study, brain MRI data showed that a non-negligible proportion of patients (12.3%) had baseline acute and old ischemic lesions but no IAT case presented with hemorrhagic transformation. The incidence of embolic infarction after IAT (25.8%) was comparable with that of silent embolic events (23%) following diagnostic angiography and intervention,[40] indicating that IAT for CRAO did not carry an increased risk in comparison to conventional diagnostic and interventional angiography. However, silent infarction can be a precursor of symptomatic stroke and is also associated with progressive brain damage and vascular dementia.[41] These adverse neurologic reactions should be carefully considered in the context of clinical decision-making.

Our study has several limitations. The retrospective nature of this study introduces inherent possibilities of bias, especially selection bias, because it is difficult to control bias and confounders in retrospective studies. In particular, the time between CRAO onset and treatment could not be controlled in this study. Although not statistically significant, the time from onset to treatment tended to be longer in the ST

group, which may have affected our results. However, our main finding of a significant difference in visual outcome between the IAT and ST groups in incomplete CRAO may not have resulted from the longer period between CRAO onset and treatment in the ST group. Among the patients with incomplete CRAO, the period was actually longer in the IAT group than in the ST group. Therefore, although the time from CRAO onset to treatment could not be controlled, our study suggests that IAT may be helpful in visual outcome when used for incomplete CRAO.

Furthermore, the sample size was not sufficient for subgroup comparative analyses among patients with incomplete and total CRAO. The inclusion of patients who refused IAT into the ST group is another weakness in our study design. Direct comparisons of our results with those of previous studies are difficult because our study had a different treatment protocol, inclusion criteria, and visual improvement parameters. Finally, variability in the follow-up period of each patient can be another source of bias when considering the evaluation of final visual outcome.

In conclusion, IAT may have the advantage of early retinal reperfusion in eyes with acute CRAO and significant efficacy in visual restoration in those with incomplete CRAO. However, the adverse events revealed by clinical examinations and brain MRI indicate that IAT should be performed cautiously and selectively.

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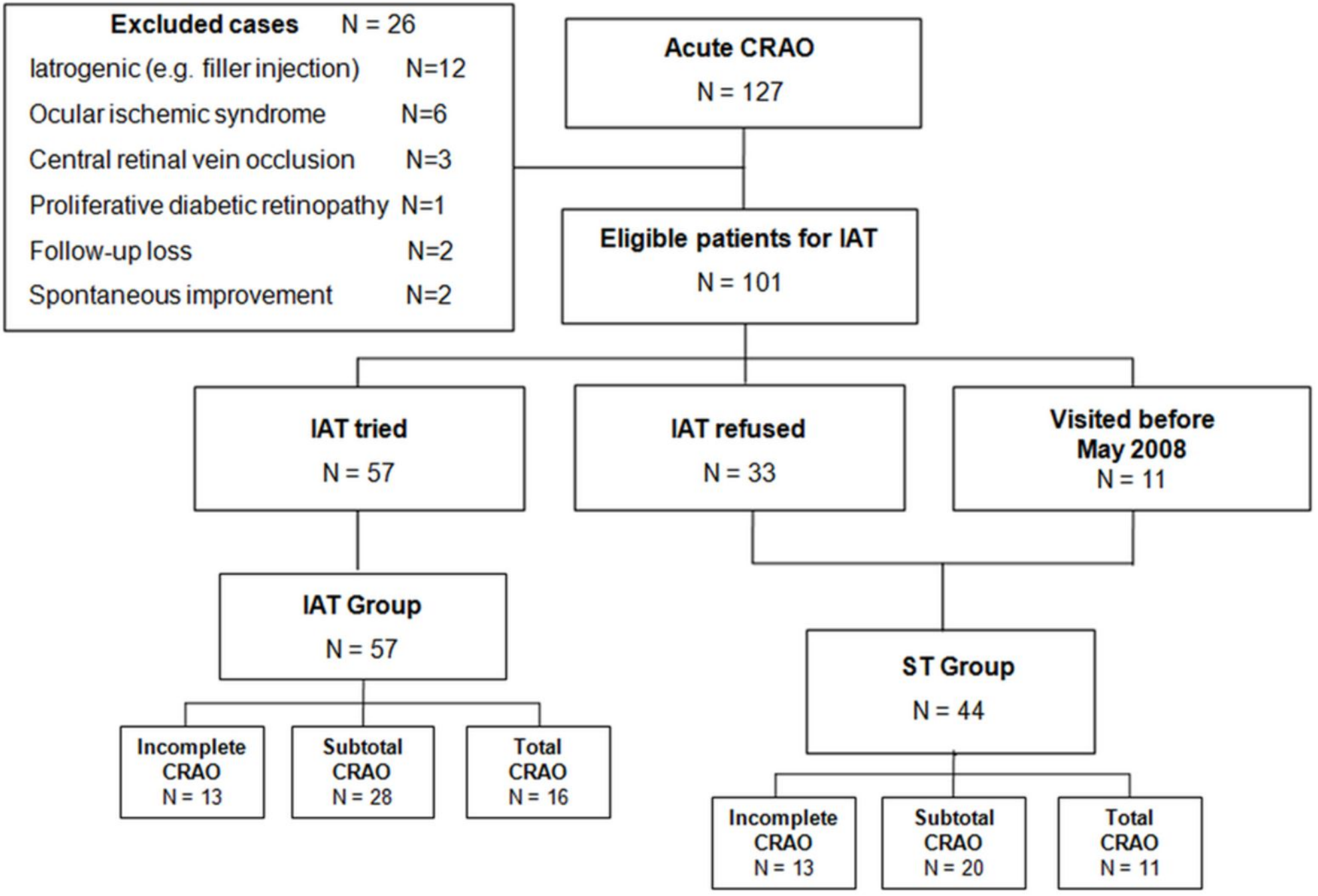
FIGURE LEGENDS

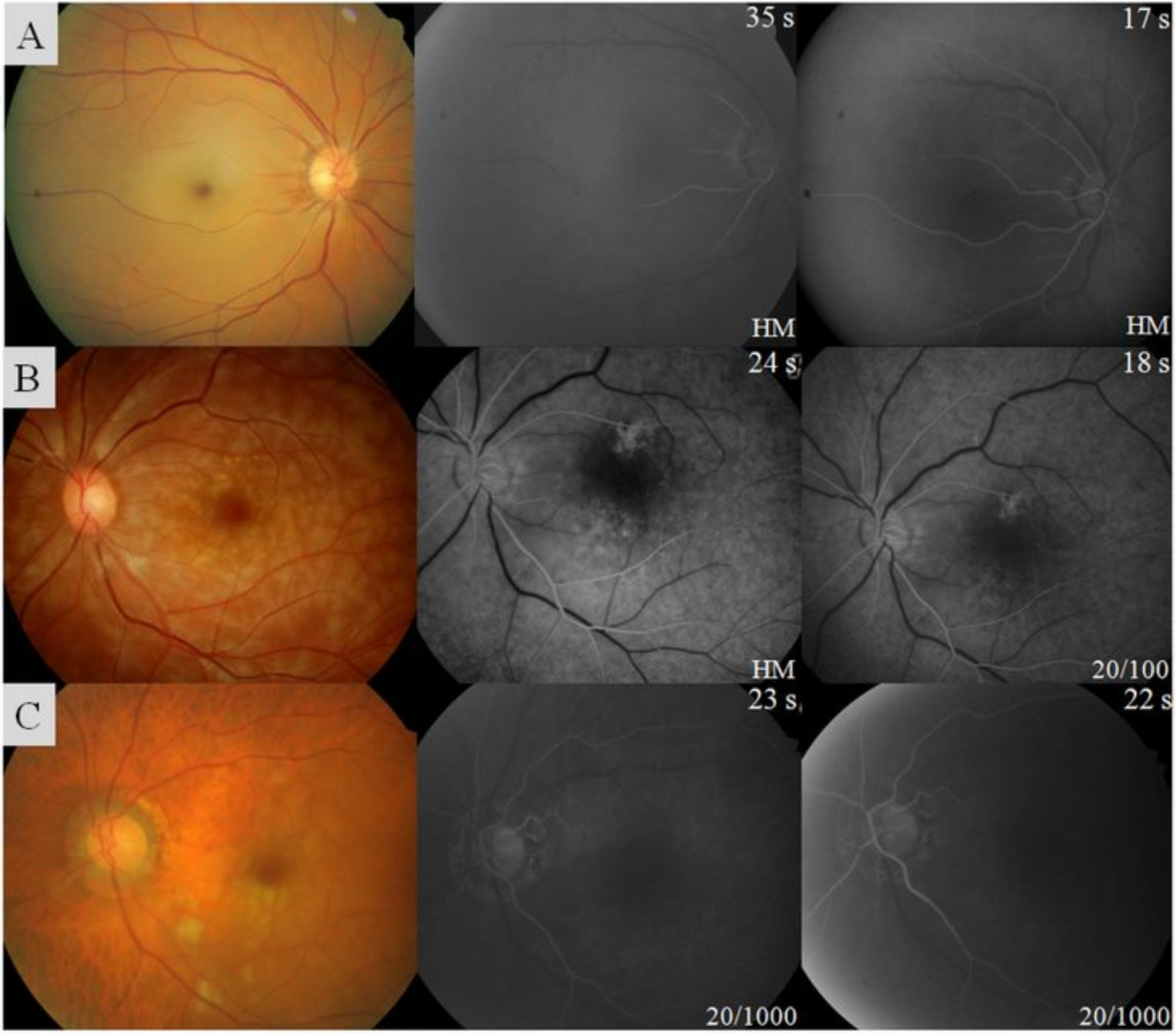
Figure 1. A flow chart showing our study design and patient inclusion/exclusion criteria. CRAO = central retinal artery occlusion; ST = standard treatment; IAT = intra-arterial thrombolysis

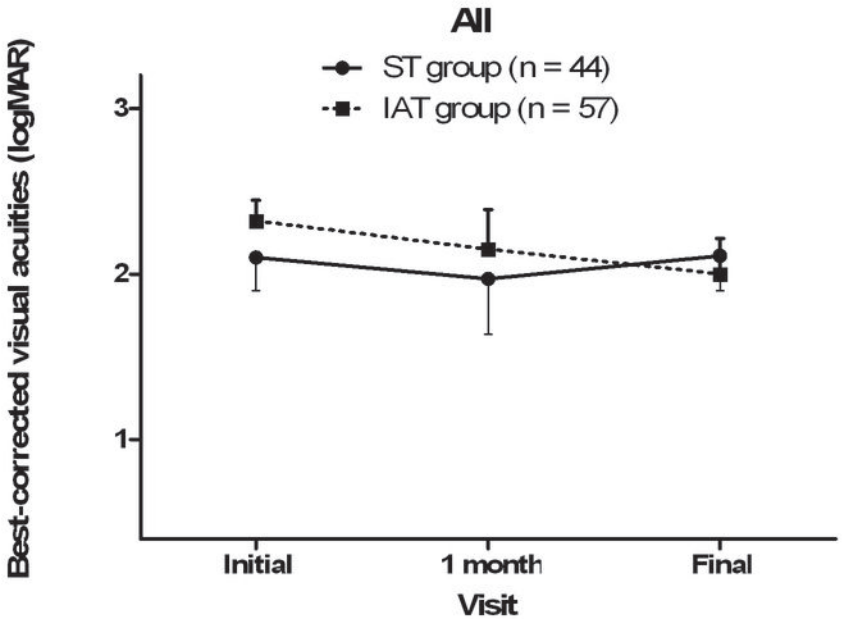
Figure 2. The fundus photograph (left column) and fluorescein angiographs obtained before and 1 day after treatment (middle and right columns) for representative cases of subtotal (A) and incomplete (B, C) central retinal artery occlusion (CRAO). The text in the upper right corner indicates the time at which images were taken; those in the lower right corner denote best-corrected visual acuity. The 75-year-old man in (A) and the 62-year-old man in (B) showed anatomic success (early reperfusion) after intra-arterial thrombolysis. Visual acuity in the eye with subtotal CRAO (A) was hand motion (HM) at both the first visit and 1 month after the IAT, whereas that with incomplete CRAO (B) improved from counting fingers (CF) to 20/100. In the 74-year-old man with incomplete CRAO treated with standard treatment (C), there was no improvement in either visual acuity (stable at 20/1000) or retinal perfusion.

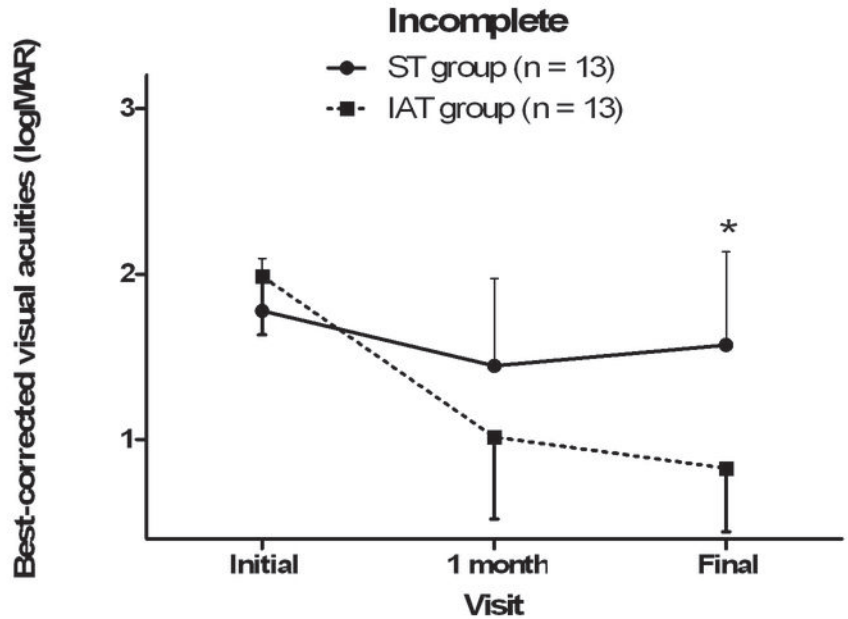
Figure 3. The temporal pattern of best-corrected visual acuity (BCVA) in the intra-arterial thrombolysis (IAT) and standard treatment (ST) groups among all patients with CRAO and those with incomplete, subtotal, and total CRAO. Error bars denote upper or lower bound of 95% confidence intervals. An asterisk (*) denotes statistical significance ($P < 0.05$).

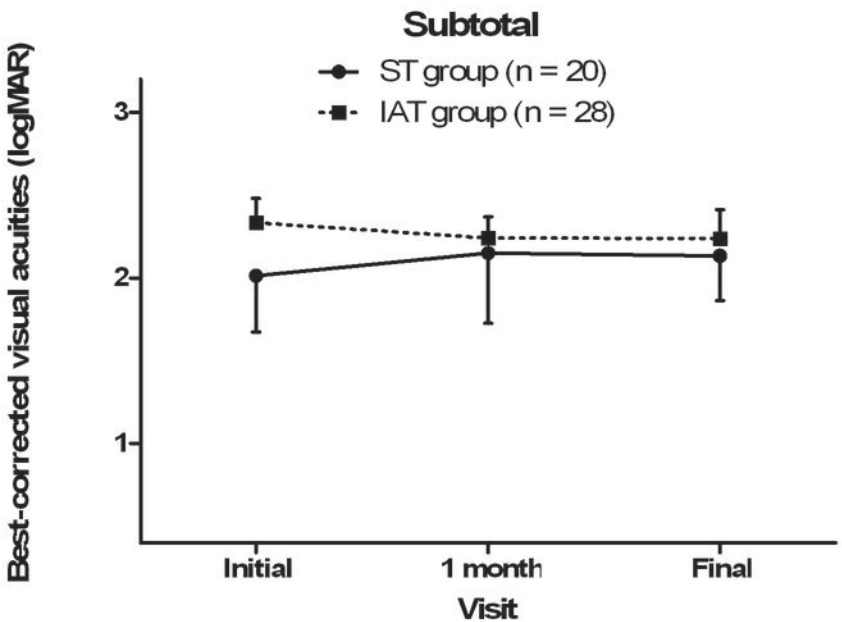
Figure 4. The percentages of (A) best-corrected visual acuity (BCVA) ≥20/200 and (B) clinically significant visual improvement (≥0.3 logMAR) in the intra-arterial thrombolysis (IAT) and standard treatment (ST) groups among all patients with CRAO and those with incomplete, subtotal, and total CRAO.

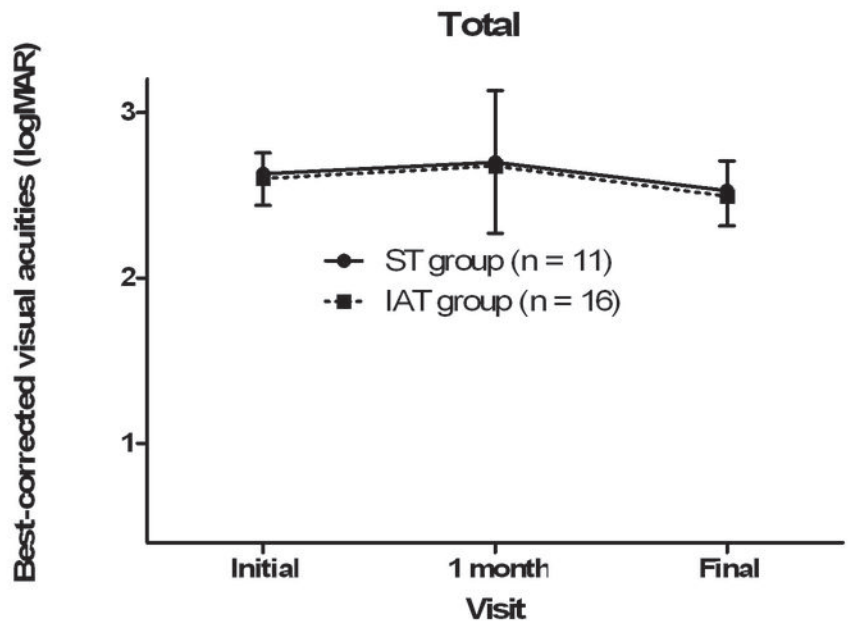

Excluded cases N = 26
Iatrogenic (e.g. filler injection) N=12
Ocular ischemic syndrome N=6
Central retinal vein occlusion N=3
Proliferative diabetic retinopathy N=1
Follow-up loss N=2
Spontaneous improvement N=2
Acute CRAO
N = 127
Eligible patients for IAT
N = 101
IAT tried
N = 57
IAT refused
N = 33
Visited before May 2008
N = 11
IAT Group
N = 57
Incomplete CRAO
N = 13
Subtotal CRAO
N = 28
Total CRAO
N = 16
ST Group
N = 44
Incomplete CRAO
N = 13
Subtotal CRAO
N = 20
Total CRAO
N = 11


A
35 s
17 s
HM
HM
B
24 s
18 s
HM
20/100
C
23 s
22 s
20/1000
20/1000


All
ST group (n = 44)
IAT group (n = 57)
Best-corrected visual acuities (logMAR)
3
2
1
Initial
1 month
Final
Visit


Incomplete
ST group (n = 13)
IAT group (n = 13)
*
Best-corrected visual acuities (logMAR)
3
2
1
Initial
1 month
Final
Visit


Subtotal
ST group (n = 20)
IAT group (n = 28)
Best-corrected visual acuities (logMAR)
3
2
1
Initial
1 month
Final
Visit


Total
ST group (n = 11)
IAT group (n = 16)
Best-corrected visual acuities (logMAR)
3
2
1
Initial
1 month
Final
Visit

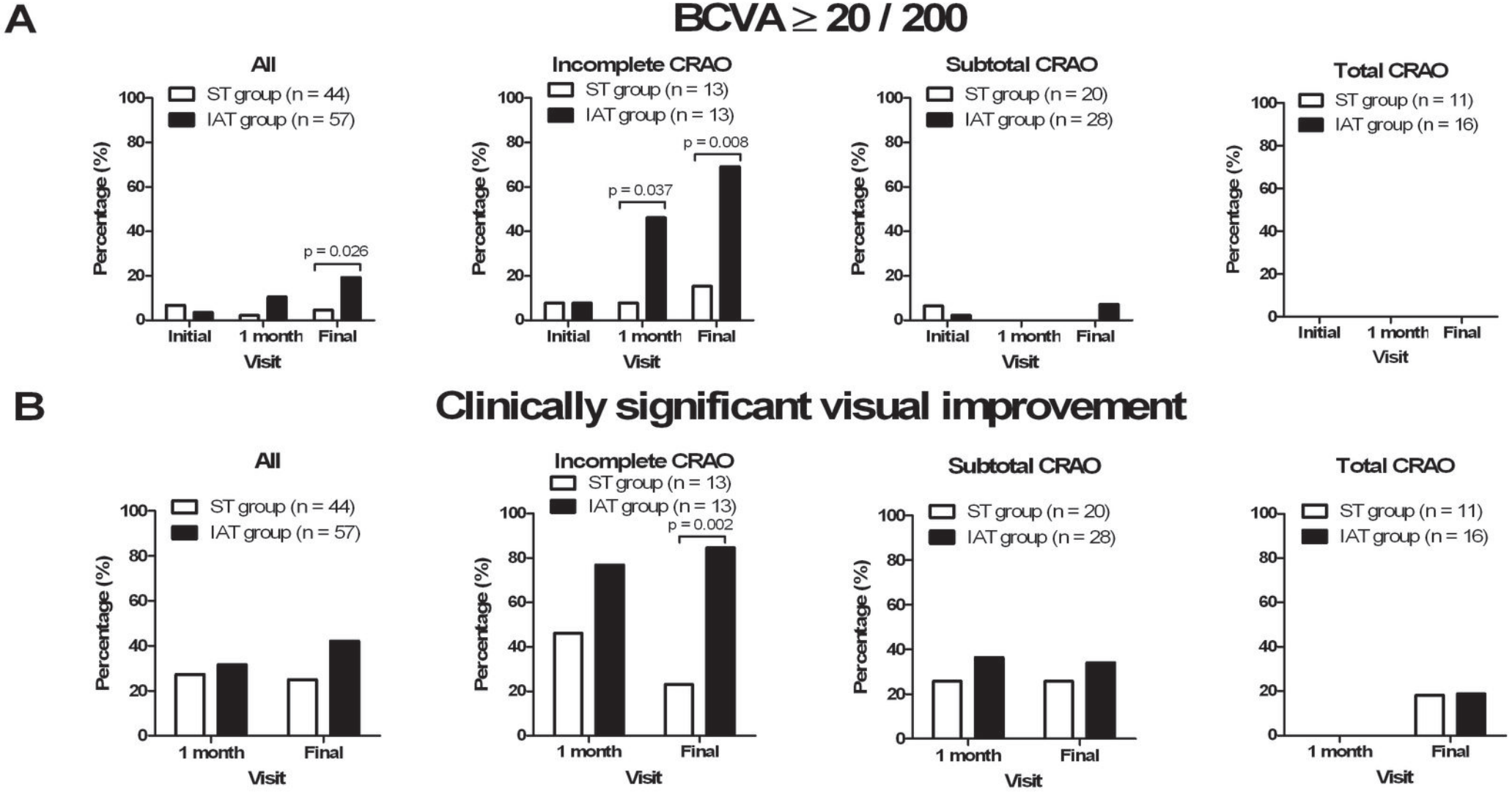

A
BCVA ≥ 20 / 200
All
ST group (n = 44)
IAT group (n = 57)
p = 0.026
Incomplete CRAO
ST group (n = 13)
IAT group (n = 13)
p = 0.037
p = 0.008
Subtotal CRAO
ST group (n = 20)
IAT group (n = 28)
Total CRAO
ST group (n = 11)
IAT group (n = 16)
Percentage (%)
Initial
1 month
Final
Visit
B
Clinically significant visual improvement
All
ST group (n = 44)
IAT group (n = 57)
Incomplete CRAO
ST group (n = 13)
IAT group (n = 13)
p = 0.002
Subtotal CRAO
ST group (n = 20)
IAT group (n = 28)
Total CRAO
ST group (n = 11)
IAT group (n = 16)
Percentage (%)
1 month
Final
Visit

Table 1. Inclusion and exclusion criteria of subjects.

Inclusion criteria	1) Non-arteritic CRAO 2) Symptom duration ≤ 24 hours (In incomplete CRAO[8], ≤ 7 days) 3) BCVA ≤ 20/63 (Snellen) 4) Follow-up period ≥ 1 month
Exclusion criteria	**Ocular factor or disease** 1) Spontaneous improvement of vision or retinal perfusion at initial presentation (<4 hours after symptom onset) 2) Branch retinal artery occlusion 3) Combined central retinal vein occlusion 4) Suspicious ocular ischemic syndrome 5) Central retinal artery occlusion from iatrogenic cause 6) Combined ocular pathologies interfering visual outcome (i.e. diabetic macular edema)
	Systemic conditions restricting thrombolysis 1) Uncontrolled hypertension (systolic blood pressure >200 mmHg) 2) Coagulation disorder 3) A history of heart attack, intracranial hemorrhage, cerebral infarction, or intracranial surgery within 3 months 4) Intracranial hemorrhage in brain magnetic resonance images at baseline 5) Current anti-thrombotic treatment 6) A history of allergic reaction to contrast agent 7) Unable to undergo thrombolysis for carotid and ophthalmic artery obstruction

BCVA = best corrected visual acuity; CRAO = central retinal artery occlusion.

Table 2. Comparison of demographic and clinical characteristics between the intra-arterial thrombolysis (IAT) and standard treatment (ST) groups.

	IAT group	ST group	*P*
Number of patients	57	44	N/A
Mean age, years (range)	58.3 ± 14.7 (18-79)	64.5 ± 17.4 (19-90)	0.054
Male : Female	36 : 21	29 : 15	0.775
Time from symptom onset to treatment, hours (range)	22.7 ± 30.6 (1-172)	35.9 ± 27.6 (2-120)	0.054
Incomplete CRAO (n = 26)	50.5 ± 54.3 (9-172)	29.7 ± 26.8 (4-34)	0.391
Subtotal CRAO (n = 48)	16.4 ± 11.2 (3-42)	40.5 ± 30.3 (2-120)	**0.011**
Total CRAO (n = 27)	11.2 ± 6.4 (1-23)	33.0 ± 25.5 (5-72)	**0.034**
Mean follow-up period, month (range)	9.9 ± 12.4 (1-55)	13.3 ± 19.2 (1-74)	0.308
Mean initial visual acuity, LogMAR (range)	2.32 ± 0.47 (0.52-2.9)	2.10 ± 0.66 (0.22-2.9)	0.065
Stage, incomplete : subtotal : total	13 : 28 : 16	13 : 20 : 11	0.742

CRAO = central retinal artery occlution; LogMAR = logarithmic minimum angle of resolution; N/A = not applicable

Table 3. Comparison of overall anatomic and visual outcomes between the intra-arterial thrombolysis (IAT) and standard treatment (ST) groups.

	IAT group (n = 57)	ST (n = 44)	*P*
Visual outcome			
Mean amount of visual improvement at 1 month, LogMAR	0.13 ± 0.46	0.05 ± 0.44	0.519
Mean amount of visual improvement at the final visit, LogMAR	0.31 ± 0.63	0.08 ± 0.51	0.062
No. of eyes with BCVA ≥20/200 at 1 month (%)	6 (10.5)	1 (2.3)	0.108
No. of eyes with BCVA ≥20/200 at the final visit (%)	11 (19.3)	2 (4.5)	**0.026**
No. of eyes showing clinically significant visual improvement* at 1 month (%)	18 (31.6)	12 (27.3)	0.639
No. of eyes showing clinically significant visual improvement* at the final visit (%)	24 (42.1)	11 (25)	0.056
Anatomic outcome			
No. of eyes showing early (≤3 days) reperfusion / No. of FA performed (%)	40 / 54 (74.1)	12 / 28 (42.9)	**0.005**
No. of eyes showing final (1 month) reperfusion / No. of FA performed (%)	45 / 51 (88.2)	25 / 31 (80.6)	0.346

BCVA = best corrected visual acuity; FA = fluorescein angiography; LogMAR = logarithmic minimum angle of resolution

* Visual improvement ≥0.3 LogMAR

Table 4. Comparison of demographic data, baseline clinical characteristics, and treatment outcomes between the intra-arterial thrombolysis (IAT) and standard treatment (ST) groups according to the stage of central retinal artery occlusion (CRAO).

	Incomplete CRAO (N=26)		*P**	Subtotal CRAO (N=48)		*P†*	Total CRAO (N=27)		*P**
	IAT group (n=13)	ST group (n=13)		IAT group (n=28)	ST group (n=20)		IAT group (n=16)	ST group (n=11)	
Mean age	60.5 ± 10.8	64.3 ± 14.6	.461	56.4 ± 17.4	67.0 ± 13.4	**.027**	59.9 ± 12.7	60.5 ± 25.9	.945
Male: Female	8:5	10:3	.336	17:11	15:5	.301	11:5	4:7	.102
Mean time from symptom onset to treatment, hours	50.5 ± 54.3 (9-172)	29.7 ± 26.8 (4-34)	.391	16.4 ± 11.2 (3-42)	40.5 ± 30.3 (2-120)	**.011**	11.2 ± 6.4 (1-23)	33.0 ± 25.5 (5-72)	**.034**
Mean initial BCVA, LogMAR (range)	1.93 ± 0.58 (20/60-HM)	1.78 ± 0.52 (20/60-HM)	.532	2.43 ± 0.37 (20/150-NLP)	2.23 ± 0.67 (20/400- NLP)	.082	2.60 ± 0.29 (HM-NLP)	2.63 ± 0.28 (HM-NLP)	.810
Visual Outcome									
Mean visual improvement at 1 month, LogMAR (range)	1.08 ± 0.21 (0.40-1.9)	0.23 ± 0.26 (-0.30-1.3)	**<.001**	0.03 ± 0.40 (-1.4-0.9)	-0.03 ± 0.40 (-1.4-1.1)	.689	0.04 ± 0.11	0.04 ± 0.11	.926
Mean visual improvement at final visit, LogMAR (range)	1.08 ± 0.53 (0-1.6)	0.08 ± 0.57 (-0.3-1.3)	**<.001**	0.10 ± 0.53 (-1.4-1.1)	0.07 ± 0.60 (-1.5-1.2)	.890	0.11 ± 0.36	0.10 ± 0.27	.961
No. of the eyes with 1-month BCVA ≥20/200 (%)	6 (46.2)	1 (7.7)	**.037**	0	0	N/A	0	0	N/A
No. of the eyes with final BCVA ≥20/200 (%)	9 (69.2)	2 (15.4)	**.008**	2 (7.1)	0	.335	0	0	N/A
No. of the eyes with clinically significant visual improvement at 1 month‡ (%)	10 (76.9)	6 (46.2)	.113	4 (14.3)	4 (20)	.442	0	0	N/A
No. of the eyes with clinically significant visual improvement at final visit‡ (%)	11 (84.6)	3 (23.1)	**.002**	7 (25)	5 (25)	.628	3 (18.8)	2 (18.2)	.684
Anatomic outcome									
No. of early (≤3 days) reperfusion / No. of FA performed	11/11 (100)	5/9 (55.6)	**.026**	21/28 (75)	6/11 (54.5)	.194	8/15 (53.3)	1/8 (12.5)	.069

No. of final (1 month) reperfusion / No. of FA performed	11/11 (100)	5/8 (62.5)	.058	21/25 (84)	13/15 (86.7)	.600	13/15 (86.7)	7/8 (87.5)	.731

FA = Fluorescein angiography; HM = hand motion; NA = not applicable; NLP = no light perception

Amount of visual improvement = final LogMAR visual acuity – initial LogMAR visual acuity

* P values were obtained using Fisher's exact test for dichotomous variables and Mann-Whitney *u* test for continuous variables.

† P values were obtained using chi-square test for dichotomous variables and Student's *t* test for continuous variables.

‡ Visual improvement ≥0.3 LogMAR

Table 5. Neurological and non-neurological adverse reactions after intra-arterial thrombolysis in patients with central retinal artery occlusion

	No. of patients / No. of MRI or exam performed (%)
Neurological adverse reactions after IAT	
Embolic infarction*	8 / 31 (25.8)
Symptomatic neurological deterioration†	1 / 57 (1.8)
Intracranial hemorrhage	0 / 31
Transient ischemic attack	0 / 31
Death related to any neurologic problem	0 / 57
Non-neurological non-ocular adverse reactions after IAT	
Hematoma at vessel puncture sites	2 / 57 (3.5)
Headache	1 / 57 (1.8)
Tinnitus	1 / 57 (1.8)
Hyperesthesia	1 / 57 (1.8)
Treatment-associated infection	0
Anaphylaxis	0
Renal dysfunction	0
Ocular adverse reactions after IAT	
Increased intraocular pressure	2 / 57 (3.5)

* Asymptomatic in 7 patients, symptomatic in 1 patient

† Hemianopsia which recovered completely in 7 days