# Local Intra-arterial Fibrinolysis and the Effects of Time to Treatment in Central Retinal Artery Occlusion: A Systematic Review

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**ABSTRACT**

**Objective:** Conventional regimens in central retinal artery occlusion have been ineffective in reversing visual loss. Local intra-aterial fibrinolysis(LIF) has shown promising results. The aim of this study was to review data on LIF with directed emphasis on the effect of time interval to treatment on visual outcome to obtain an idea on the time frame within which fibrinolysis would yield worthwhile results.

**Methods:** We systematically reviewed studies published after year 2000 on LIF. After correction for data duplication, the results of LIF in 44 patients with complete data are reported.

**Results:** Mean interval to LIF was 18.7 hours (SD 37.2), range 4–240 hours. 43.2% of patients had an improvement of 2-Snellen lines or more with 25% achieving 6/15 or better and 34.1% attaining 6/60 or better 48 hours post-intervention. Treatment instituted within 6 hours from symptom onset resulted in a mean improvement of 5.4 lines compared to 2 lines in patients treated beyond 6 hours. When presenting acuity was light perception or worse, only 1 in 10 eyes attained a 2-line improvement even with intervention within 10 hours. Complications were seen in 5 patients (11.4%) and included intracerebral haemorrhage (1), ischaemic cerebrovascular accident (2), transient ischaemic attack (1) and vitreous haemorrhage (1).

**Conclusion:** Retrospective studies show potential benefits of LIF especially if administered within 6 hours from symptom onset. The studies had methodological limitations and in the absence of randomised controlled trials, there is insufficient evidence to justify its routine use in view of notable systemic events.

*Keywords:* CRAO, fibrinolytic therapy, systematic review

## INTRODUCTION

The natural course of central retinal artery occlusion (CRAO) often leaves the affected eye legally blind. Commonly used conventional regimens such as intraocular pressure lowering and attempts at inducing retinal vasodilatation have generally been ineffective in reversing visual loss[1–4] with only 20–35% of eyes retaining useful vision. The natural history of CRAO left only 20% of eyes retaining a final visual acuity (VA) of 6/30 or better in a study published in 1999[5].

With increasing experience and beneficial results of fibrinolytic therapy in coronary and peripheral artery occlusions, attempts have been made to extend its use to the treatment of CRAO. A meta-analysis of all the published data before the year 2000 on local intra-arterial fibrinolysis (LIF) summarised the visual outcome of 100 patients from 16 studies with results suggesting a benefit of intra-arterial thrombolysis compared to conventional treatments or the natural history of retinal artery occlusion[6]. However, changes in VA were found to be unrelated to the time to intervention in the analysis.

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Table 1. Summary of included studies

| Authors | Size | Study Design | Intervention | |
|---|---|---|---|---|
| Vallee *et al* | 11 | Case series<br>Retrospective | LIF using urokinase<br>Pre and post treatment FFA performed to assess circulatory reperfusion | |
| Butz *et al* | 22 | Case series<br>Retrospective | LIF using urokinase or rtPA<br>No pre and post treatment FFA | |
| Pettersen *et al* | 8 | Case series<br>Retrospective | LIF using<br>No pre and post treatment FFA | 1 pt with BRAO excluded from analysis |
| Riccardo *et al* | 3 | Case series<br>Retrospective | LIF using<br>Pre and post treatment FFA performed | |

We systematically reviewed studies published since the last meta-analysis in year 2000 with directed emphasis on treatment criteria and visual outcomes in order to analyse the effect of time interval from presentation to intervention on visual improvement and ascertain the relationship between initial VA and final visual outcome.

## METHODS

Thirteen reports of intra-arterial fibrinolysis for CRAO were identified in the published literature after correction for data duplication from the meta-analysis published in year 2000[7–19]. Series with full patient profile, details of time to intervention and proper documentation of pre and post intervention VA were included in our analysis. Studies with incomplete data and patients with cilioretinal artery sparing or branch retinal artery occlusion were excluded. The first randomised controlled trial (RCT) for LIF in CRAO is currently in the process of patient recruitment.

The fibrinolytic treatment involved the insertion of a guiding catheter into the internal carotid artery via the femoral artery and coaxial advancement of a microcatheter into the origin of the ophthalmic artery. In cases where there was preexisting occlusion of the internal carotid artery, treatment was carried out via the maxillary-ophthalmic anastomoses. Local fibrinolysis was followed by intravenous heparinisation for a period of 2–3 days.

On follow-up, measurements of VA at 24 to 48 hours post treatment, fundoscopic examination, visual field assessment and in some studies, pre and post treatment fundal fluorescein angiography (FFA) were carried out.

Analysis was performed using Revman 4.2 software.

## RESULTS

After correction for data duplication and exclusion of series with incomplete data, the findings of 44 patients from 4 case series[7–10] were combined and analysed. The included studies are summarised in Table 1. Age at presentation ranged from 40 to 84 years with a mean of 63.5 (SD 11.5). The male to female ratio was 25:19. Mean interval to LIF was 18.7 hours (SD 37.2), range 4–240 hours. Eighteen patients (41%) received urokinase and 26 (59%) received recombinant tissue plasminogen activator (rtPA). The majority of patients presented with severe visual loss with only 5 eyes (11.4%) presenting with acuity better than 6/60 (Table 2).

Final acuities ranged from 6/6 to NPL. Nineteen (43.2%) patients had an improvement of 2 Snellen lines or more with 14 (31.8%) attaining post-treatment VA of 6/30 or better, and 9 (20.5%) achieving post intervention acuity of 6/12 or better. Of the 3 (6.8%) patients who achieved post-treatment acuity of 6/6, 2 had presenting acuity better than 6/60. The last patient had CF presenting vision and was treated 12 hours

Table 2. Characteristics of study population.

| Pt no | Age | Gender | Diagnosis | Time to fibrinolysis (hours) | Initial VA worse than 6/60 | Initial VA better than 6/60 | VA at 24-48 hours | VA change (Snellen lines) | Agent used | Cx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 56 | F | CRAO+CRVO | 12 | CF | | CF | 0 | Urokinase | VH |
| 2 | 45 | F | CRAO+CRVO | 12 | CF | | 6/30 | 5 | Urokinase | |
| 3 | 47 | M | CRAO+CRVO | 240 | | 6/15 | 6/6 | 4 | Urokinase | |
| 4 | 66 | F | CRAO+CRVO | 12 | CF | | 6/12 | 9 | Urokinase | |
| 5 | 69 | F | CRAO+CRVO | 72 | | 6/15 | 6/9 | 2 | Urokinase | |
| 6 | 67 | M | CRAO+CRVO | 48 | | 6/45 | 6/15 | 5 | Urokinase | |
| 7 | 53 | M | CRAO+CRVO | 48 | 6/120 | | 6/15 | 7 | Urokinase | |
| 8 | 58 | F | CRAO+CRVO | 12 | CF | | 6/60 | 2 | Urokinase | |
| 9 | 51 | M | CRAO+CRVO | 48 | CF | | 6/120 | 1 | Urokinase | |
| 10 | 44 | M | CRAO+CRVO | 48 | CF | | CF | 0 | Urokinase | |
| 11 | 45 | M | CRAO+CRVO | 12 | CF | | 6/6 | 12 | Urokinase | |
| 12 | 68 | M | CRAO | 8 | HM | | 6/120 | 2 | rtPA | |
| 13 | 67 | M | CRAO | 9 | HM | | CF | 1 | rtPA | |
| 14 | 75 | M | CRAO | 18 | HM | | CF | 1 | rtPA | |
| 15 | 59 | F | CRAO | 10 | HM | | HM | 0 | rtPA | |
| 16 | 71 | F | CRAO | 8.5 | CF | | CF | 0 | rtPA | |
| 17 | 77 | M | CRAO | 8 | LP | | LP | 0 | rtPA | |
| 18 | 76 | M | CRAO | 6 | HM | | HM | 0 | rtPA | |
| 19 | 70 | F | CRAO | 8 | LP | | CF | 2 | rtPA | |
| 20 | 78 | M | CRAO | 6.75 | NPL | | NPL | 0 | Urokinase | |
| 21 | 44 | F | CRAO | 8.25 | NPL | | NPL | 0 | rtPA | |
| 22 | 84 | F | CRAO | 7.5 | NPL | | NPL | 0 | Urokinase | CVA |
| 23 | 71 | M | CRAO | 8.25 | LP | | LP | 0 | Urokinase | |
| 24 | 69 | F | CRAO | 4 | LP | | LP | 0 | rtPA | |
| 25 | 69 | M | CRAO | 10 | LP | | LP | 0 | Urokinase | |
| 26 | 46 | F | CRAO | 7.5 | HM | | HM | 0 | rtPA | |
| 27 | 75 | M | CRAO | 5 | HM | | HM | 0 | Urokinase | |
| 28 | 71 | M | CRAO | 11 | HM | | HM | 0 | rtPA | |
| 29 | 74 | F | CRAO | 8 | HM | | HM | 0 | rtPA | CVA |
| 30 | 51 | M | CRAO | 10 | HM | | HM | 0 | rtPA | |
| 31 | 65 | F | CRAO | 9.5 | HM | | HM | 0 | rtPA | |
| 32 | 70 | M | CRAO | 9.5 | CF | | HM | -1 | rtPA | |
| 33 | 62 | M | CRAO | 8 | LP | | HM | 1 | Urokinase | |
| 34 | 77 | M | CRAO | 6.25 | LP | | HM | 1 | rtPA | ICH |
| 35 | 72 | F | CRAO | 8 | HM | | 6/120 | 2 | rtPA | |
| 36 | 45 | M | CRAO | 7 | HM | | 6/120 | 2 | rtPA | |
| 37 | 65 | F | CRAO | 8 | HM | | 6/120 | 2 | rtPA | TIA |
| 38 | 65 | M | CRAO | 7 | | 6/12 | 6/9 | 1 | Urokinase | |
| 39 | 66 | M | CRAO | 6.25 | 6/120 | | 6/18 | 6 | rtPA | |
| 40 | 61 | F | CRAO | 6 | CF | | 6/9 | 10 | rtPA | |
| 41 | 40 | F | CRAO | 4.75 | | 6/36 | 6/6 | 8 | rtPA | |
| 42 | 76 | M | CRAO | 6.5 | CF | | 6/18 | 7 | rtPA | |
| 43 | 62 | M | CRAO | 4.5 | CF | | 6/9 | 10 | rtPA | |
| 44 | 70 | M | CRAO | 4.5 | CF | | 6/9 | 10 | rtPA | |

CRVO = central retinal vein occlusion; CF = counting fingers; HM = hand movement; LP = light perception; NPL = no light perception; rtPA = recombinant tissue plasminogen activator; Cx = complications; VH = vitreous haemorrhage; CVA = cerebrovascular accident; ICH = intracranial haemorrhage; TIA = transient ischaemic attack

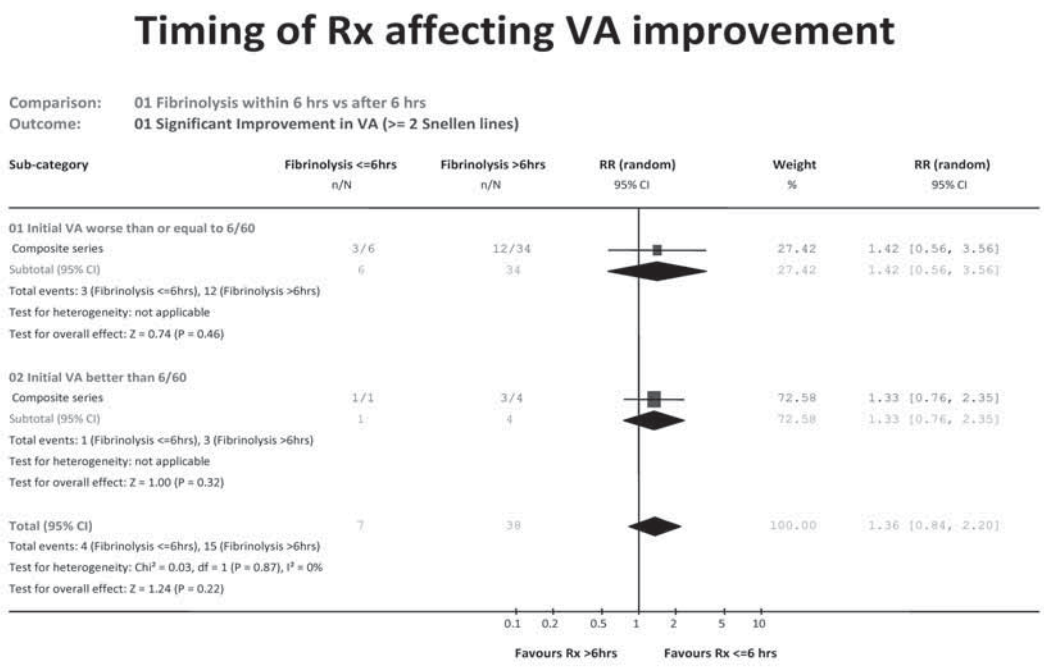


Fig. 1. Timing of treatment versus achievement of significant VA improvement (at least 2 lines).

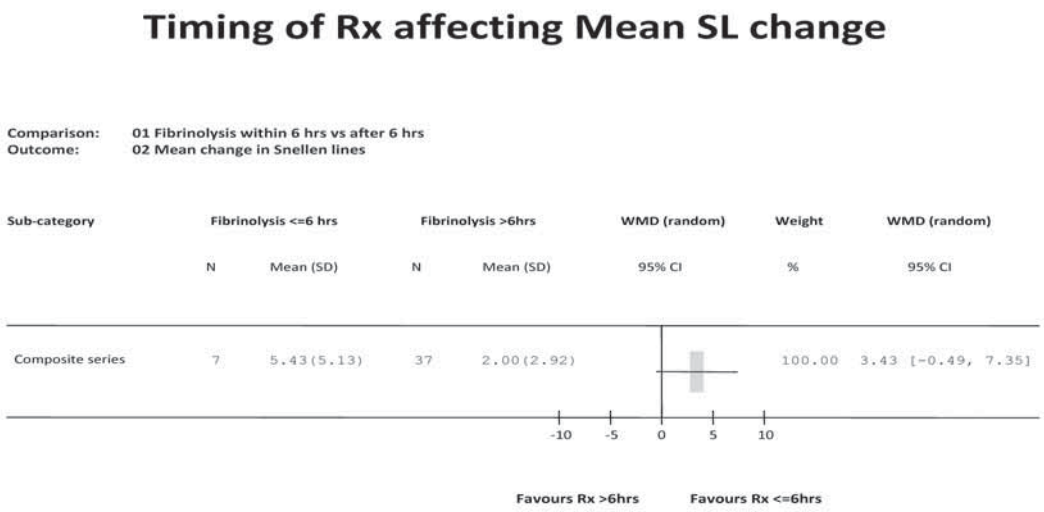


Fig. 2. Timing of treatment versus mean Snellen line change.

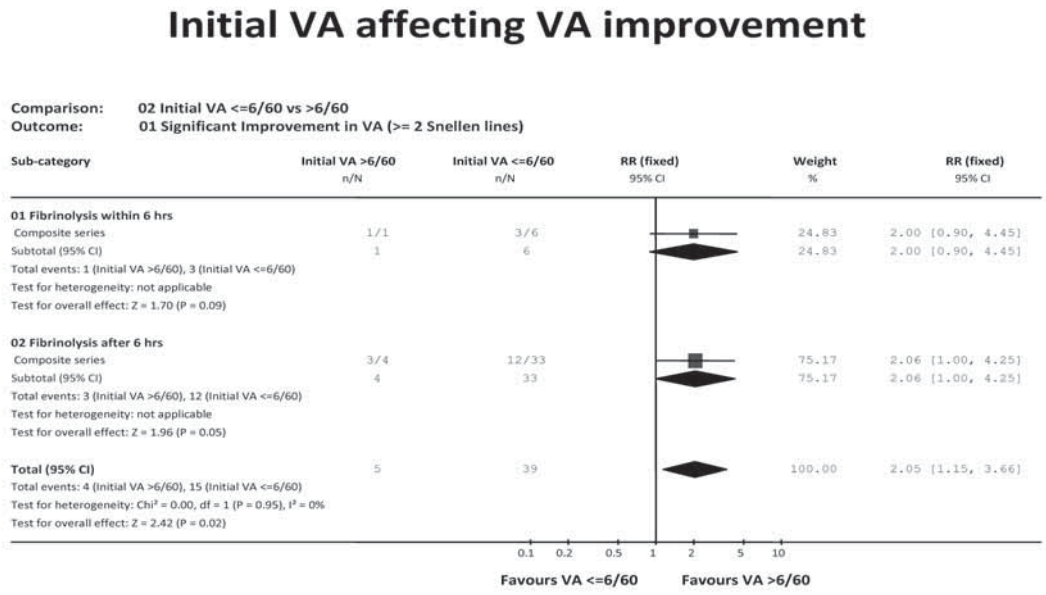


Fig. 3. Initial VA versus achievement of significant VA improvement (at least 2 lines).

after symptom onset. None of the patients presenting with HM vision or worse had improvement to better than 6/120 vision.

Using Revman 4.2 analysis software, after controlling for initial VA as a confounding factor using stratified analysis, time to intervention of 6 hours and less resulted in 1.4 times the chance of having VA improvement of 2 or more Snellen lines and 3.4 lines greater mean improvement. (Fig. 1) Treatment instituted within 6 hours from symptom onset resulted in a mean improvement of 5.4 lines compared to 2 lines in patients treated beyond 6 hours (Fig. 2).

We also found initial VA of 6/60 or worse to be a poor prognostic factor (p=0.02) for visual improvement. Initial acuity better than 6/60 resulted in 2 times the chance of achieving VA improvement of 2 or more Snellen lines (Fig. 3) with a mean improvement of 4 lines compared to 2.4 lines for patients presenting with 6/60 or worse. (Fig. 4, overleaf) When presenting acuity was light perception or worse, only 1 in 10 eyes attained a 2 line improvement even with intervention within 10 hours.

Complications were seen in 5 patients (11.4%) and included intracerebral haemorrhage (1), ischaemic cerebrovascular accident (2), transient ischaemic attack (1) and vitreous haemorrhage (1).

**DISCUSSION**

The time window for fibrinolysis in CRAO remains undetermined and is taken with analogy to stroke. The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke study published that systemic fibrinolysis within 3 hours after symptom onset in stroke patients was associated with better outcomes[20]. It can still be beneficial up to 6 hours[21].

Histologic and electrophysiologic studies in animal eye models suggest that irreversible ischaemic retinal damage develops after 100 minutes of experimentally produced complete CRAO[22]. If there were a moderate amount of residual circulation in the retina via anastomotic

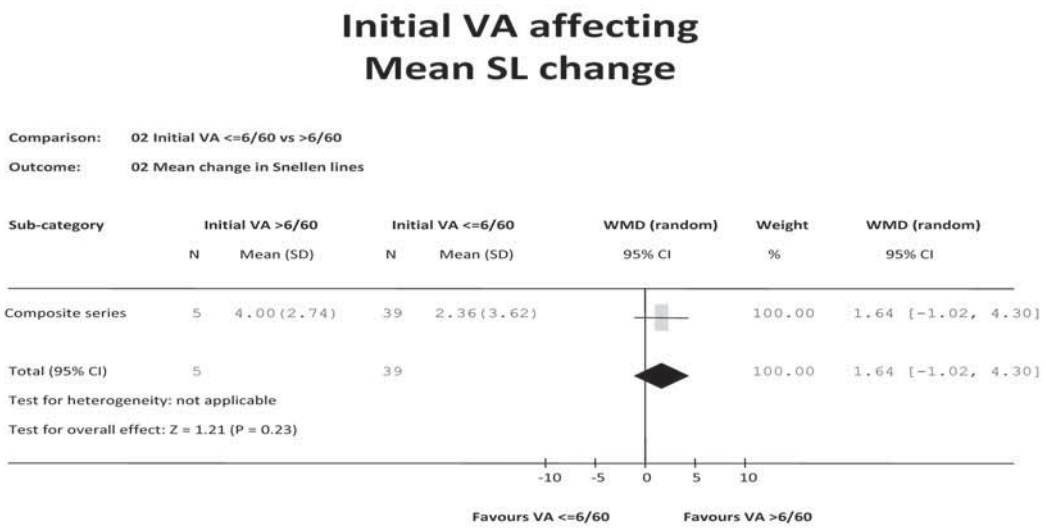


Fig. 4. Initial VA versus mean Snellen line change.

channels, the retina can survive up to a maximum of 3 to 4 hours[23]. There have been clinical reports of improvement in vision in patients treated beyond this time frame up to as late as 3 days post onset, but this may be due to incomplete occlusion or the presence of a cilioretinal artery. The efficacy of fibrinolytic therapy is limited beyond the ischaemic penumbra with retinal survival time probably up to a maximum of 4 hours.

There have been previously reported findings of a lack of correlation between time to intervention and visual outcome, which is inconsistent with scientific data. Our analysis shows that better results were achieved with early treatment within 6 hours from symptom onset. Although a stratified analysis controlling for initial VA as a potential confounding factor did not reach statistical significance due to the small numbers, the benefit of early treatment was consistent across the strata.

We included a case series with combined CRAO and Central Retinal Vein Occlusion (CRVO) in our analysis. As development or resolution of macular oedema in CRVO affects final acuity and may distort the contributory effects of LIF, we compared only the VA at 24 to 48 hours after intervention with pre-treatment VA. These patients also had objective FFA evidence of improved retinal arteriovenous transit time. Ten of 11 patients in this series presented within 72 hours from symptom onset, well before formation of collaterals could be established to cloud the issue.

There is a point of contention as to the scientific rationale for the use of fibrinolytic agents in cases of CRAO secondary to emboli that consist largely of cholesterol or calcium. Arruga and Sanders found that only 15.5% of retinal emboli were composed of fibrinoplatelet material, whilst 74% consisted of cholesterol and 10.5% of calcium[24]. As fibrinolytic agents have no effect on cholesterol or calcium, fibrinolysis has been viewed by some authors to be appropriate for only a small group of patients[5]. However, there is a postulated role for fibrinolytic agents in lysis of secondary thromboemboli that form as a result of the induced stasis causing progression of the arterial occlusion[25] thus making it still of benefit beyond the group with fibrinoplatelet emboli. The mechanical effect of flushing during LIF has also been postulated to assist in restoring patency.

The success rates of LIF in individual studies have been reported to be between 7.3 and 43.5%[4,6,26–31]. Our

finding of 43.2% of patients having an improvement of 2 Snellen lines or more and 32% of eyes achieving a post treatment VA of 6/30 or better compare favourably with the natural history of CRAO[5] (reported rate of 20% with final acuity of 6/30 or better) and with conventional forms of therapy such as the use of carbogen therapy[32–34], globe massage[2,4,35], topical beta-blockers and acetazolamide to reduce intraocular pressure[1,2,4], and anterior chamber paracentesis[1,4,36]. The reported success rates for these therapies ranged between 15–21% when the criteria for visual improvement was taken to be at least 2 Snellen lines with rates in individual retrospective studies varying between 6 and 49%[3].

There are methodological limitations in our analysis as the studies analysed were small, retrospective and non-randomised with no control groups. There was also no standardisation in the patient selection process, the fibrinolytic agents used and measurement of visual improvement. The interval between symptom onset and treatment was large, ranging from 4 to 240 hours. Two of the studies had no standardised pre and post lysis FFA assessment to objectively assess for residual perfusion before initiation of treatment and improvement of circulation after therapy. The patients with better presenting acuity may have had incomplete occlusions or presence of a cilioretinal artery predisposing them to better visual recovery. Learned eccentric fixation could also account for improved VA unless VA measurements are made by trained staff.

The risk of complications is significant at 11.4%, with other studies reporting rates of between 3.2–12%[6,26–31] and include life-threatening conditions like intracerebral haemorrhage, transient ischaemic attacks or strokes from catheter manipulation-induced emboli. In view of the life-threatening risks involved, the use of fibrinolytic therapy cannot be recommended in advance of a well-designed randomised study. The first multi-centre RCT evaluating LIF in CRAO is currently in the stages of patient recruitment in Europe[11].

Some patients with very poor presenting vision of counting fingers or worse showed visual improvement after treatment, giving hope to an otherwise dismal condition. We recognise the significant adverse effects associated with reported studies, but this may be at an early stage and is also very dependent on individual interventional neuroradiologists. As this new modality of treatment seems to suggest some hope in recovering some useful vision, perhaps combining this with careful patient selection may provide the best possible outcome in these patients.

## CONCLUSION

Retrospective studies show potential benefits of LIF especially if administered within 6 hours from symptom onset but with notable systemic adverse events. In cases where therapy is to be instituted, the potential systemic complications need to be thoroughly discussed with the patient. The results of the multi-centre RCT evaluating LIF in CRAO are awaited, and until then, LIF treatment for patients with CRAO needs to be evaluated carefully for potential gains versus the risk of systemic complications.

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