Is Management of Central Retinal Artery Occlusion the Next Frontier in Cerebrovascular Diseases?

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Dear Dr. José Biller, MD, Editor (*Journal of Stroke and Cerebrovascular Diseases*),

I was interested to read the long review article by Limaye and colleagues entitled "Is management of central retinal artery occlusion the next frontier in cerebrovascular diseases?"[1]

I have done comprehensive studies on: (a) anatomy of 100 central retinal and 59 ophthalmic arteries, and (b) experimental central retinal artery occlusion (CRAO) studies in 101 eyes of rhesus monkeys, and (c) clinical studies on all aspects of 260 CRAO eyes. Based on that knowledge, I find the review article by Limaye and colleagues contains misleading information, wrong citations of the literature, and cited references not in a sequential order but in haphazard fashion. To discuss all these flaws, even briefly, would require several pages, which is impossible in a letter to the editor. But the article introduces misleading and distorted information on multiple aspects of CRAO, which require comment. Here are just a few examples.

1. The authors cited some of my studies, but several of those references are not relevant to the implied topics, or wrongly cited. For example, to support of various statements dealing with the central retinal artery (CRA) they cite an article of mine which deals with the optic nerve head circulation and not at all with what the authors imply.
2. I did a comprehensive anatomical study of 100 CRA and 59 ophthalmic arteries; but their anatomical descriptions about them are misleading. For example, they state: "The central retinal artery (CRA) is the terminal branch of ophthalmic artery", but the terminal branches of the ophthalmic artery are dorsal nasal and supratrochlear arteries. Moreover, their cited references 2 and 3 are not relevant.
3. Their references 14 and 15, about narrowest diameter of the CRA, do not deal with that topic; reference 13 does, because it deals with origin and course of CRA, but not with CRAO.
4. They stated that a cilioretinal artery is seen in 20%; however, first, there is a wide variation in the reported incidence of the number of cilioretinal arteries in an eye; second, they cited my study dealing with the origin and course of the CRA, which has nothing to do with what the authors imply.
5. I first classified CRAO into 4 categories in my study of 260 eyes. They have copied that classification, without referring to my original article; moreover, they make several mistakes in that, apart from totally irrelevant references. They mention serotonin causing transient vasospasm of the CRA, which was discovered by our study (which they did not cite), and not by the papers cited by them.
6. The authors support their following statements: "there is no consensus on treatment as the opinions vary about the best approach and the duration of the time window to establish reperfusion to save vision." with references to 3 of my studies – none of which deals with treatment of CRAO.
7. For differentiation of CRAO from anterior ischemic optic neuropathy, they cited my study dealing with the natural history of visual outcome.
8. Their Figure 1 represents acute CRAO with cilioretinal artery sparing, and not just acute CRAO.
9. In Figure 2 they show iris neovascularization, which they claim is a complication of CRAO.

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In my studies, I showed that that can develop only if CRAO is associated with ocular ischemic syndrome or diabetic retinopathy, and not CRAO *per se*.

10. The authors state: "The long-term treatment of patients with CRAO is similar to those with stroke or heart disease"; this is also implied by title of their review: "Is management of central retinal artery occlusion the next frontier in cerebrovascular diseases?" They all are neurologists, who have done no studies on CRAO, and due to a lack of in-depth knowledge of CRAO, they have equated CRAO with ischemic stroke; this is not only irrational but represents a fundamental flaw in the entire concept presented in this review. Retina and brain are very different in their morphology, physiology, and response to acute ischemia and reperfusion, as is evident from the following. Briefly, my experimental study[2] in 38 rhesus monkeys showed that if CRAO lasts for an hour or less and circulation is restored, the retina suffers no permanent ischemic damage; after that, the longer the CRAO, the greater the ischemic damage, and if CRAO lasts 4 hours, it produces irreversible ischemic retinal damage. The tolerance time of the brain to acute ischemia by contrast is much shorter. Briefly, the reasons for that are these:

    (a) The brain has very scanty stores of intracellular glucose and depends entirely on the blood circulation to supply constantly not only oxygen but also glucose. In the retina by contrast, (i) there is an ample store of glucose and glycogen in the Mùller cells. (ii) The vitreous' glucose content is 3 times that of the retina. (iii) Probably the most important factor is that the choroidal vessels supply the major part of glucose and oxygen. This gives the retina self-sufficiency in glucose, and to some extent in oxygen, for much longer than the brain.

    (b) Development of edema of the neural tissue in acute ischemia is well-established. When this occurs in the brain due to acute ischemia, (i) the rigid cranial cavity cannot accommodate the extra volume produced by brain edema, and (ii) since the brain is composed of thick, solid tissue, ischemic edema markedly compresses the brain tissues. These two factors combine to cause obliteration of the microvasculature, resulting in a "no-reflow phenomenon", which prevents recirculation. That explains irreversible brain damage after even transient brain ischemia. The retina, on the other hand, is a very thin membrane, set in surroundings which can accept mild edema easily, so no "no-reflow phenomenon" exists. Hence the striking difference in the ischemic tolerance times.

11. The authors have equated amaurosis fugax with transient ischemic attack. I have done a comprehensive study on amaurosis fugax in 209 eyes. That showed that that is not a valid concept, because transient ischemic attack is cerebral in origin, whereas amaurosis fugax is ophthalmic in origin, and is not always due to transient retinal ischemia; it does occur in optic nerve head transient ischemia and other ocular diseases but not cerebral in origin.
12. My study[3] on systemic diseases in 234 patients with CRAO showed that embolism is the most common cause of CRAO. The vital action is to reduce the risk of that to prevent further visual loss and stroke. Hyperlipidemia is the major risk factor, because it produces atherosclerosis and plaques in the carotid artery, the major source of embolism. Other sources of embolism are cardiac valvular lesions.
13. Finally, the authors discussed the role of thrombolysis in CRAO. Reputable studies by Beatty and Au Eong,[4] Fraser and Siriwardena,[5] Noble et al.,[6] Framme et al.[7] and a prospective, randomized, multicenter clinical trial in 84 CRAO patients by Schumacher et al.[8] conclusively showed that local intra-arterial fibrinolysis not only has no beneficial effect but also can be associated with serious systemic complications. Limaye and colleagues countered that by mentioning the Johns Hopkins Hospital study[9] in 42 patients, half treated by local intra-arterial t-PA study (Local intraarterial fibrinolysis (LIF)) and the rest no therapy; that study claimed that LIF administered in aliquots is associated with an improvement in visual acuity compared with standard therapy and has few side effects. However, that study presents problems: (a) the treatment was given 15 hours

after the onset of CRAO, but my experimental study[2] showed that CRAO lasting for 4 hours results in irreversible ischemic retinal damage. (b) My natural history studies in 260 eyes showed that the visual outcome very much depends upon the type of CRAO, and their sample size of 21 was far too small to rule that out.

In my review[10] of the role of intra-arterial thrombolysis in CRAO, I concluded that intra-arterial thrombolytic therapy can possibly be beneficial, but only if it is started aggressively in much less than 4 hours from the onset of CRAO, and the occlusion is caused by a fibrin embolus and not by cholesterol or calcific embolus, because thrombolytic therapy cannot dissolve calcific and cholesterol emboli.

Yours sincerely,
S.S. Hayreh

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