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Review Article

A Review on the Use of Microwire for Induction of Focal Cerebral Ischemia in Rat

Siamak Sandoghchian Shotorbani[a], Seyyed Mehdi Vatandoust[b], Hajar Ogbaei[c], Sara Razzaghi[d], Javad Mahmoudi[b]*

[a]*Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[b]*Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[c]*Department of physiology, Tabriz University of Medical Sciences, Tabriz, Iran.*
[d]*Faculty of Veterinary Medicine, Islamic Azad University, Tabriz, Iran.*

Correspondence

Javad Mahmoudi
Neurosciences Research Center, Tabriz University of Medical Sciences Tabriz, Iran.
Tel: +984133351284
Fax: +984133340730
Email: mahmoudij@tbzmed.ac.ir

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Abstract

Within the last four decades, attempts have been made to develop reliable preclinical models of ischemic stroke with the aim of discovering its underlying mechanisms and developing novel therapeutic approaches. The middle cerebral artery occlusion (MCAo) technique in rats is able to replicate ischemic stroke with clinical relevance. Induction of MCAo through transfemoral approach using microwire permits researchers to occlude the middle cerebral artery more exactly and safely. Therefore, utilization of this technique reduces animal's morbidity and mortality, maximizes animal welfare, and minimizes the number of animals required for a study. This article aims to provide a brief overview of problems associating with the induction of MCAo by conventional methods and proposing solutions based on using microwire under fluoroscopic view in the rat.

Keywords: *Middle cerebral artery occlusion, Ischemic stroke, Microwire, Rat.*

Introduction

Occlusion of middle cerebral artery (MCA) as an accepted method is used to imitate ischemic stroke insults [1-3] in animals such as rodents, rabbits, felines, nonhuman primates [4], sheep [5] and pigs [6,7]. Rats with low purchase and husbandry costs, availability and similarities of cerebrovascular system to the human are ideal for induction of MCA occlusion (MCAo) among these animals [8,9]. Moreover, various technical facilities, imaging methods [10], methodological improvements [11-13] and behavioral assessments have been developed for precise analysis of neuronal consequences of ischemic stroke in rats. Permanent intracranial occlusion of the MCA has been used since 1975 [14,15]. In this technique, mechanical occlusion of MCA using diathermy or ligation of the proximal MCA, induces ischemic stroke. Because, it inevitably needs to craniotomy, it may cause some complications such as alteration of intracranial pressure, disruption of blood brain barrier [10,16]. To cope with these problems and achieve minimally invasive model, Koizumi and co-workers introduced the first rat model of indirect MCAo in 1986 [17]. In this method, a filament (inserted into lumen of internal common carotid artery (ICA) either through the ipsilateral external common carotid artery (ECA) or common carotid artery) occludes MCA opening in circle of Willis and results in induction of ischemic injury [18,19]. In comparison to permanent MCAo technique, this offers minimal invasive model and obviates the need for craniotomy. However, factors such as high incidence of mortality [8], occurrence of subarachnoid hemorrhage (SAH) [16] due to cerebral vessels perforation, significant risk for early mortality after 24 to 48 hours [20] as well as variable and incomplete MCAo (8, 16) reduce its reliability and reproducibility.

In order to refine MCAo, image-guided method for induction of MCAo have been introduced in rats. In this method, under fluoroscopic guidance, a microwires that is so called polymer jacket-on-core is advanced through femoral artery in to the middle cerebral artery territory [11]. Induction of MCAo by polymer jacket-on-core is benefited from the flexible and radiopaque nitinol (nickel-titanium alloy) made microwire with a polymer jacket covering its distal tip. The utilization of this method, not only provides a reliable and repeatable technique

for induction of ischemic stroke, but also facilitate exact and controllable occlusion of MCA in rats [11]. Because of the less invasive nature of this procedure, mortality and morbidity occur less than conventional MCAo methods. Therefore, it improves animal welfares and reduces the number of animals required for a study [21]. This review article aims to discuss about some problems associating with conventional MCAo methods and presents solutions on the basis of using microwire under fluoroscopic view for induction of ischemic stroke in rat.

Occluder considerations

The nature of filament and its quality have important role in increasing MCAo efficacy and avoiding inadvertent intracranial hemorrhage [8]. Given this, many attempts have been made to optimize and design different types of filaments in a way that improves this model effectiveness and minimizes its associated risks. Importantly, occluders which are used in MCAo method can be categorized as coated filaments and bare filaments. To produce coated filaments, different materials such as poly-L-Lysine, silicon rubber, nail polish and methyl methacrylate glue have been used to cover its surface and improve some of its physical characteristics. However, variations in MCAo outcomes as well as SAH occurrence still remain common dilemma among researchers [22]. Contrary to these types of occluders, ploymer jacket-on-core microwire provides a reliable occluder for induction MCAo in rodents and not only reduces SAH during MCAo but also increases the success rate of surgery [11,21].

Visualization considerations

Lack of direct visualization to follow up inserted filament and uncertainty in the correct filament placement are important problems that cause premature occlusion and/or perforation of ICA lumen which subsequently result SAH [23]. In addition, most of human strokes affect 4.5% to 14% of the ipsilateral hemisphere whereas; conventional intraluminal method results in cortical and subcortical infarcts that include approximately 21% to 45% of affected hemisphere [24,25]. So, high degree of variability in infract size and its location, largely to blind advancing of occluder, remains a major pitfall that can reduce repeatability and reproducibility of this method. Importantly, conventional MCAo method occludes blood flow in the posterior communicating artery and results in infarction in regions such as hypothalamus, hippocampus and substantia nigra. Hence, animals experience some degrees of life threating events including: elevated body temperature, impaired water homeostasis, and paresis [25].

Laser-Doppler Flowmetery (LDF) is commonly used for real-time monitoring of blood flow in the MCA territory to verify adequacy of the MCAo and reperfusion [26]. However, LDF only indicates relative decline in blood flow at only a single region, and it cannot be used for monitoring of entire ischemic territory and determining of incomplete or full occlusion of MCA [24]. Additionally, this method is roughly invasive and needs stereotaxic surgery for correct placement of LDF probe over the skull [8].

Applying guided fluoroscopy to real time navigation of endovascular microwire from the femoral artery to the MCA opening [11], provides exploratory visualization tools without stereotaxic surgery for monitoring of the entire occlusion territory and improves the MCAo sensitivity in a way that exactly and selectively occludes different MCA territories [25].

Approach considerations

Conventional MCAo technique requires identification and isolation of CCA, ICA and ECA through a ventral midline cervical incision [27]. As an important concern the separation of these arteries from the adjacent tissues can induce mechanical trauma to the cervical ganglions, sympathetic trunk, and vagus nerve. Consequently, stimulation of these nerves leads to acute cardiac arrhythmia, myocardial ischemia and even left ventricular heart failure during the surgery procedure [8,9].

Also, insertion of occluder through ECA causes complications including cerebral blood flow augmentation in the filament-inserted hemisphere [11], artery spasm that makes resistance against advancing of the inserted filament [23] and interruption of blood flow to the nervous and muscular structures supplied by ECA [23,28]. Indeed, permanent ligation of ECA results in irreversible damages of masticatory and hypopharyngeal muscles [25], which consequently impairs function of mastication and swallowing in animals with ischemic stroke. This results in decreased food and water intake in rats [28], disturbed MCAo outcomes and occurrence of problems that may influence neurological and behavioral evaluations [11]. Notably, insertion of jacket-on-core microwire through transfemoral approach avoids CCA permanent ligation and preserves the ECA [11,21].

In conclusion, techniques based on using microwires and application of fluoroscopic guidance for induction of cerebral artery occlusion may provide reliable approaches for induction of MCAo. Moreover, designing precise studies based on using different types of microwires seems to be necessary for development of this emergent techniques.

Conflict of interest

The authors declare that they have no conflict of interest.

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