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Research paper

A new middle cerebral artery occlusion model for intra-arterial drug infusion in rats

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HIGHLIGHTS

- We developed a device to block MCA and deliver drugs intra-arterially in rats.
- The effectiveness of the device in inducing stroke rivaled that of suture method.
- Compared to existing methods, the device enhanced the efficiency of drug delivery.
- Using this device, drugs could be delivered with or without reperfusion.
- A second surgery and the complex catheterization were avoided by using this device.

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ABSTRACT

With the wide application of intra-arterial therapy for cerebrovascular disorders, preclinical intra-arterial drug-delivery studies based on middle cerebral artery occlusion (MCAO) models have become urgent. In the present study, a novel stroke model was developed for intra-arterial drug delivery: MCAO and drug delivery were accomplished using a microcatheter device. MCAO was induced in Sprague-Dawley rats using the microcatheter device (cMCAO group, $n = 10$) or a nylon suture (sMCAO group, $n = 10$). After 24-h occlusion, neurological deficit and infarct volume were compared between the groups. Drug-delivery models used in stroke studies were compared with the present model to verify the drug-delivery ability of the microcatheter device. MCAO was induced using the microcatheter device in 21 Sprague-Dawley rats. At 4 h after occlusion, 2% Evans blue dye was infused using different methods, and 1 h later, the dye was extracted from each hemisphere and spectrophotometrically quantified. All cMCAO group rats showed neurological deficits; none developed subarachnoid hemorrhage or died before sacrifice. Neurological deficits and infarct volumes were similar in the cMCAO and sMCAO groups. Significantly more dye leakage occurred in the ischemic hemispheres of the rats that received the dye *via* the microcatheter device. Compared to other intra-arterial drug-delivery models used in stroke studies, the present model was easily established, had a high success rate, caused minimal surgical injury, and enabled highly efficient drug delivery. Thus, the present model is an efficient tool for investigating the effect of intra-arterial drug delivery on ischemic cerebral tissue.

1. Introduction

The rodent middle cerebral artery occlusion (MCAO) model [8,17] created using a nylon filament inserted into the internal carotid artery (ICA) is widely used to investigate the mechanisms underlying ischemic stroke. Compared with systemic administration, intra-arterial drug injection results in high local drug concentration and reduces systemic adverse effects [3]. Recently, preclinical studies have investigated intra-arterial drug delivery in MCAO models [1,4,6,13].

The existing MCAO models for intra-arterial drug infusion have inherent drawbacks. The model described by Ding et al. [6] resulted in unstable establishment due to the use of modified polyethylene (PE)-50 catheters. Moreover, in this model, the drug is delivered only after the catheter or suture has been withdrawn, resulting in reperfusion. Thus, this model is mainly limited to reperfusion studies, and is not suitable for investigating neuroprotection in case of

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permanent MCAO. In the models described by Song et al. [13] and Van Winkle et al. [15], drug delivery was independent of reperfusion: MCAO was induced using a nylon suture, while the drug was delivered *via* a catheter lodged in the common carotid artery (CCA). However, this complex surgery was time consuming and resulted in additional injuries. Also, the intra-arterial drug inevitably entered the pterygopalatine artery, rendering the estimation of the amount of drug entering the ischemic hemisphere difficult.

In the present study, an attempt was made to develop a novel stroke model for intra-arterial drug delivery: MCAO and drug delivery were accomplished using the same microcatheter, and drugs could be delivered directly into the ischemic hemisphere *via* the ICA before, during, after reperfusion or without reperfusion.

2. Materials and methods

2.1. Microcatheter device design

One end of a 50-mm-long PE-0402 microcatheter [inner diameter (ID): 0.20 mm × outer diameter (OD: 0.38 mm; Anilab Software & Instruments Co., Ltd., Ningbo, China] was blocked using a 1-mm-long plug (nylon filament; OD: 0.181 mm) that was just coated with epoxide glue. Next, 2 mm from this end, a longitudinal incision (1-mm long) was carefully made in the wall of the microcatheter (Fig. 1A). The other end of the microcatheter was introduced into a PE-50 catheter (0.58 mm ID × 0.96 mm OD; Anilab Software & Instruments Co., Ltd.), so that 5 mm of its tip extended beyond the PE-50 catheter (Fig. 1B). The junction between the two catheters was fixed with epoxide glue. The PE-50 catheter worked as an adapter tube between the microcatheter and a 2-mL syringe. Finally, a guidewire (nylon filament; OD: 0.181 mm) was inserted into the microcatheter to increase the strength of the microcatheter and make it easy to get to the root of the anterior cerebral artery (ACA). Moreover, guidewire can also prevent the formation of clot in the microcatheter. A schematic drawing and photographs of the catheter device are shown in Fig. 1.

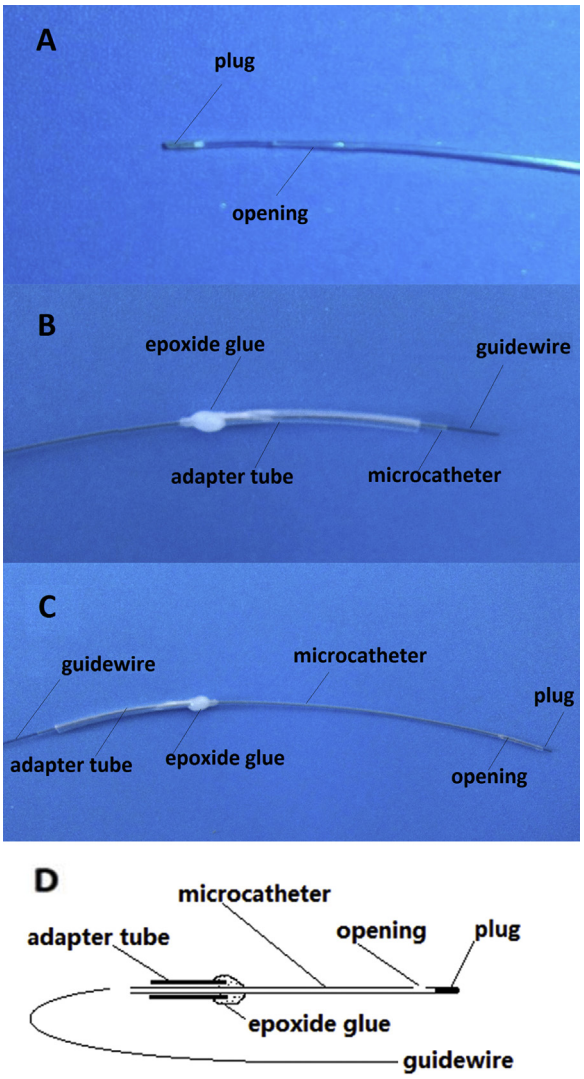

Fig. 1. Photographs (A, B, and C) and a schematic drawing (D) of the new microcatheter device.
(A) One end of the microcatheter was blocked with a plug, and 2 mm away from this end, a longitudinal incision (opening) was made in the wall of the microcatheter.
(B) The other end of the microcatheter was introduced into the adapter tube. The junction between the microcatheter and the tube was fixed with epoxide glue. A guidewire was inserted into the microcatheter.
(C and D) The microcatheter device consisted of the microcatheter, adapter tube, and guidewire.

2.2. Animal preparation

This study was approved by the Animal Care and Use Committee of the General Hospital of Shenyang Military Region, and was in accordance with the principles outlined in the National Institutes of Health Guide. A total of 41 adult male Sprague-Dawley rats (280–320 g; Department of Laboratory Animals, General Hospital of Shenyang Military Region, Shenyang, China) were used in this study.

2.3. MCAO

Twenty male Sprague-Dawley rats were used to compare the effectiveness of nylon sutures and the microcatheter device in inducing stroke after 24 h of MCAO. Sprague-Dawley rats were fasted overnight, and then, anesthesia was induced and maintained with 1–3% halothane in 70% N_2O and 30% O_2 administered *via* a face mask. A transcranial laser Doppler flowmetry (moorVMS-LDF2; Moor Instruments, Axminister, UK) was used to measure cerebral blood flow in the core MCA territory. A right femoral artery catheter was inserted to monitor mean arterial pressure, heart rate, and measure arterial gas levels and pH. In the microcatheter device MCAO group (cMCAO, $n = 10$), permanent MCAO was induced using the microcatheter device. In the nylon suture MCAO group (sMCAO, $n = 10$), permanent MCAO was induced using a commercially available nylon suture (OD: 0.28 mm; tip diameter: 0.38 mm; Beijing Cinontech Co., Ltd., Beijing, China).

The surgical procedures for MCAO using the microcatheter device and the nylon suture were identical to the MCAO protocol described by Longa et al. [8]. In brief, the left CCA, ICA, and external carotid artery (ECA) were exposed through a midline incision. A microvascular clip was placed across both the CCA and the ICA adjacent to the origin of ECA. Next, the ECA was transected to create a stump whereby the microcatheter device or nylon suture was introduced. The microvascular clip was removed, and the microcatheter device or nylon suture was gently advanced from the ECA to the ICA lumen. After the device or suture was advanced ~17 mm beyond the carotid artery bifurcation, a sharp decrease in cerebral perfusion was observed using the transcranial laser Doppler, indicating that the tip of the microcatheter or suture had reached the narrow proximal ACA, thereby blocking the MCA at its origin (Fig. 2).

2.4. Neurological examination

In a blinded manner, neurological deficits in the sMCAO group ($n = 10$) and the cMCAO group ($n = 10$) were examined after 24 h of MCAO. The deficits were scored on a modified scoring system based