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Cannulation of the internal carotid artery in mice: A novel technique for intra-arterial delivery of therapeutics

Alejandro Santillan[a,b,*,1], David G. Rubin[a,b,1], Conor P. Foley[b,c,1], Dolan Sondhi[d], Ronald G. Crystal[d], Y. Pierre Gobin[a,b], Douglas J. Ballon[b,c]

[a] Department of Neurological Surgery, Weill Medical College of Cornell University, New York, NY, United States
[b] Citigroup Biomedical Imaging Core Facility (CBIC), Weill Medical College of Cornell University, New York, NY, United States
[c] Department of Radiology, Weill Medical College of Cornell University, New York, NY, United States
[d] Department of Genetic Medicine, Weill Medical College of Cornell University, New York, NY, United States

HIGHLIGHTS

- A novel minimally invasive technique for the intra-arterial delivery of therapeutics to the mouse brain.
- This surgical technique for the delivery of agents to the murine brain includes anterograde injections into the ICA and transient ligature of the PPA and occipital arteries.
- Decrease the risk of thrombi formation, and the ability to execute advanced delivery paradigms using multiple agents over an extended period of time using a single catheter.
- This technique can be performed with minimal morbidity and high survival rates.

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ABSTRACT

We have developed a novel minimally invasive technique for the intra-arterial delivery of therapeutics to the mouse brain. CD-1 mice were anesthetized and placed in a lateral decubitus position. A 10 mm midline longitudinal incision was made over the thyroid bone. The omohyoid and sternomastoid muscles were retracted to expose the common carotid artery and external carotid artery (ECA). To maximize delivery of administered agents, the superior thyroid artery was ligated or coagulated, and the occipital artery and the pterygopalatine artery (PPA) were temporarily occluded with 6-0 prolene suture. The ECA was carefully dissected and a permanent ligature was placed on its distal segment while a temporary 6-0 prolene ligature was placed on the proximal segment in order to obtain a flow-free segment of vessel. A sterilized 169 μm outer diameter polyimide microcatheter was introduced into the ECA and advanced in retrograde fashion toward the carotid bifurcation. The catheter was then secured and manually rotated so that the microcatheter tip was oriented cephalad in the internal carotid artery (ICA). We were able to achieve reproducible results for selective ipsilateral hemispheric carotid injections of mannitol mediated therapeutics and/or gadolinium-based MRI contrast agent. Survival rates were dependent on the administered agent and ranged from 78 to 90%. This technique allows for reproducible delivery of agents to the ipsilateral cerebral hemisphere by utilizing anterograde catheter placement and temporary ligation of the PPA. This method is cost-effective and associated with a low rate of morbimortality.

1. Introduction

Intra-arterial (IA) therapy is an effective way to deliver drugs to the brain, as it is capable of attaining high concentrations of delivered agents with reduced systemic exposure and concomitant side effects (Angelov et al., 2009; Gobin et al., 2001; Neuwelt et al., 1986). We have developed a surgical technique that allows for optimal intra-arterial delivery of therapeutics in the mouse brain. The development of an effective model for carotid catheterization in mice is important due to the large number of existing disease models in mice, cost effectiveness and widespread availability. Due to

* Corresponding author at: 525 E. 68th Street, Division of Interventional Neuroradiology, Department of Neurological Surgery, New York Presbyterian Hospital, New York, NY 10065, United States. Tel.: +1 703 798 2246.
E-mail addresses: alejandrosantillanmd@gmail.com (A. Santillan), davidgeorgerubin@gmail.com (D.G. Rubin), conorpfoley@gmail.com (C.P. Foley), dos2011@med.cornell.edu (D. Sondhi), geneticmedicine@med.cornell.edu (R.G. Crystal), yvg2001@med.cornell.edu (Y.P. Gobin), djb2001@med.cornell.edu (D.J. Ballon).
[1] These authors contributed equally to this study.

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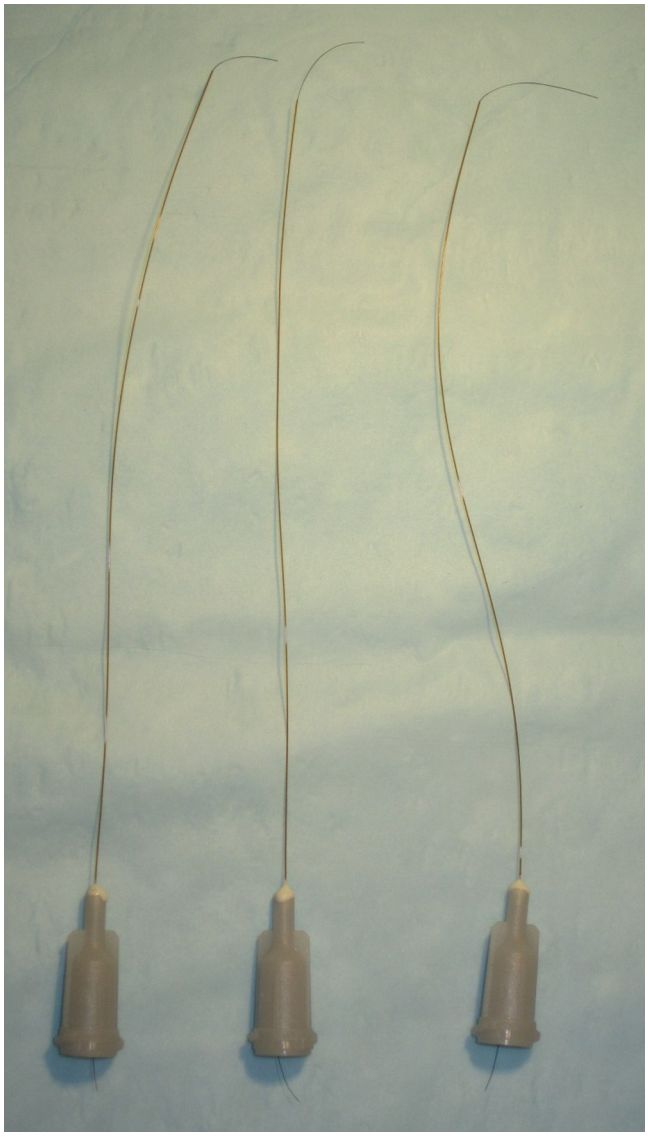

Fig. 1. Polyimide microcatheters (169 μm OD) used for intra-arterial delivery of various agents.

the similarities in vascular anatomy, this model can also be applied to rat models.

2. Materials and methods

2.1. Microcatheter fabrication

Single-thickness polyimide tubing with an outer diameter of 169 μm (MicroLumen, Tampa, FL) was cut to 10 cm lengths. One end of each segment was glued into a polypropylene luer hub (30 gauge; AmazonSupply, Seattle, WA) with Miller Stephenson 907 epoxy (Danbury, CT) and cured at 80 °C for 2 h (Fig. 1) (Zink et al., 2009). After curing, a 15-cm length of 7-0 prolene suture was passed into the lumen of the microcatheter to serve as a guidewire. This guidewire acted to keep the lumen open and prevented kinking of the microcatheter.

2.2. Operative setup

CD-1 male mice weighing 22–25 g were induced with 3% isoflurane (AErrane; Anaquest, Inc., Madison, WI) in 1–2 L/min of O_2.

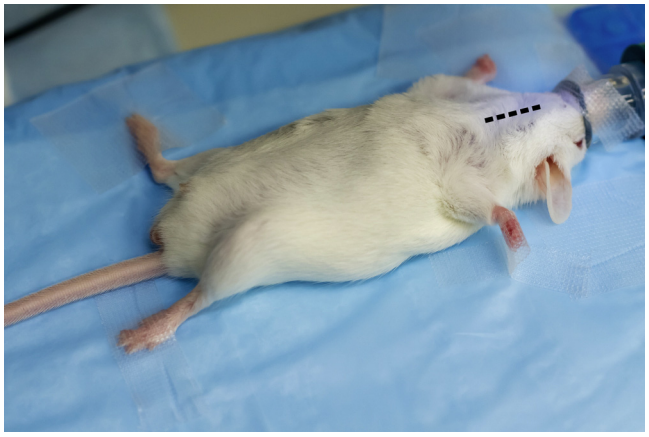

Fig. 2. Positioning of the mouse in the Kopf table. The dotted line shows a midline longitudinal incision over the thyroid bone.

The depth of the anesthesia was monitored by toe pinch. While under anesthetic, the eyes were protected with ophthalmic ointment. The animal was then placed in a lateral decubitus position and secured with tape as shown in Fig. 2. Proper positioning of the animal was crucial to achieve an adequate exposure of the neurovascular structures. The lateral decubitus position provided the best exposure of the neck muscles as well as the neurovascular structures such as the ECA, superior thyroid artery (STA), lingual artery and vagus nerve. Anesthesia was maintained with a nasal cone (VetEquip, Pleasanton, CA), with continuous 2% isoflurane in 1–2 L/min of O_2. The neck region was shaved with an electric shaver and scrubbed with alcohol. Microscissors, straight microdissecting forceps, and a needle holder were sterilized in high heat (Germinator 500, model GER-5287; Braintree Scientific, Inc.) prior to the procedure. All procedures were performed with the assistance of a surgical microscope (Omano, OM2300S-V6 Zoom Stereo Boom Microscope).

2.3. Surgical technique

A 10 mm midline longitudinal incision was made overlying the thyroid bone. The salivary glands were bluntly dissected in the midline and moved laterally using forceps and cotton tips. At this point, the following muscles were identified: omohyoid, digastric (posterior belly) and sternomastoid. The omohyoid and sternomastoid muscles as well as the left salivary gland were retracted using small fish-hook retractors to expose the common carotid artery (CCA). After exposing the carotid sheath, the distal CCA was carefully exposed using blunt dissection and microforceps to avoid injury to the STA and the nervous plexus surrounding the CCA and the external carotid artery (ECA). The ECA was exposed by elevating the hyoid bone and dissecting the cricothyroid muscle underneath. Care was taken to avoid trauma to the nervous plexus surrounding this vessel and the vagus nerve. At this point, the occipital artery, STA, lingual branch and the vagus nerve were identified (Fig. 3).

Next, the occipital artery was temporarily tied with 6-0 prolene and the STA was coagulated or ligated (Gemini Cautery System, model GEM-5917; Braintree Scientific, Inc.). The pterygopalatine artery (PPA), which represents the lateral branch of the distal ICA, was identified and temporarily tied using 10 mm of 6-0 prolene suture. The PPA was only 4–6 mm long prior to entering the skull, and care was taken to ensure that the temporary tie did not also occlude the internal carotid branch. The ECA was then carefully dissected and a flow-free vessel segment was obtained by placing a temporary ligature at the proximal ECA near the carotid bifurcation with a 10 mm 6-0 prolene suture. The distal ECA was then