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Sarah J. Messmer
University of Kentucky, sarah.goodwin2@uky.edu

Justin F. Fraser
University of Kentucky, jfr235@uky.edu

Keith R. Pennypacker
University of Kentucky, keith.pennypacker@uky.edu

Jill M. Roberts
University of Kentucky, jill.roberts@uky.edu

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Method of intra-arterial drug administration in a rat: Sex based optimization of infusion rate

Sarah J. Messmer [a,b], Justin F. Fraser [a,b,c,d,e], Keith R. Pennypacker [a,b,d], Jill M. Roberts [a,c,d,*]

[a] Center for Advanced Translational Stroke Science, University of Kentucky, 741 S. Limestone, Lexington, KY 40536, USA
[b] Department of Neurology, University of Kentucky, 741 S. Limestone, Lexington, KY 40536, USA
[c] Department of Neurosurgery, University of Kentucky, 741 S. Limestone, Lexington, KY 40536, USA
[d] Department of Neuroscience, University of Kentucky, 741 S. Limestone, Lexington, KY 40536, USA
[e] Department of Radiology, University of Kentucky, 741 S. Limestone, Lexington, KY 40536, USA

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ABSTRACT

Background: Endovascular thrombectomy is the process of removing a blood clot and re-establishing blood flow in patients with emergent large vessel occlusion. The technique provides an opportunity to deliver therapeutics directly to the site of injury. The intra-arterial (IA) route of drug administration in the mouse was developed to bridge the gap between animal stroke treatments and clinical stroke therapy. Here, we adapted the IA method for use in rats, by investigating various flow rates to optimize the IA injection through the internal carotid artery (ICA).

Methods: Male and female Sprague-Dawley rats (~4 months of age) were subjected to placement of micro-angio tubing at the bifurcation of the common carotid artery for injection into the ICA. We evaluated a range of infusion rates of carbon black ink and its vascular distribution within the brain.

Results: Optimal injection rates in males was 4–6 μl/min and 2–4 μl/min in females. The IA injection using these sex-specific rates resulted in appropriate limited dye delivery to only the ipsilateral region of the brain, without inducing a subarachnoid hemorrhage.

Conclusion: Upon adapting the IA administration model to rats, it was determined that the rate of infusion varied between males and females. This variability is an important consideration for studies utilizing both sexes, such as in ischemic stroke studies.

1. Introduction

Intra-arterial (IA) injection through the internal carotid artery (ICA) allows for a targeted delivery of therapeutics directly to the brain (Zink, Foley et al. 2009; Guo, Ge et al. 2013). Animal studies using IA injection through the ICA have been combined with an intra-luminal filament middle cerebral artery occlusion (MCAO) surgery model (Guo, Ge et al. 2013; Azedi, Mehrpour et al. 2019). The combination of IA injection and MCAO is a translational approach to mimic drug administration during an endovascular thrombectomy procedure in ischemic stroke patients.

For studies of brain injury, IA injection of compounds through the ICA allows for targeted administration without prior systemic circulation, increasing efficacy. Importantly, IA has a low mortality rate associated with the procedure (Santillan, Rubin et al. 2014). In a mouse study by Maniskas et al., the rate and volume of injection were shown to be important factors for targeted delivery (Maniskas, Bix et al. 2015). They demonstrated how different injection flow rates and volumes through the ICA of mice had either a direct, targeted delivery to the brain or a systemic delivery throughout the body. In rat studies, IA injections have been performed through the ICA (Zink, Foley et al. 2009), femoral artery (Staudacher, Sela et al. 2011), and the subclavian artery (Hayashi, Tomimatsu et al. 2006). However, there have not been any studies aimed at optimizing the injection process itself. Here, we investigated the effects of various flow rates to optimize IA injection through the ICA in male and female rats. When combined with MCAO in future studies, this would allow for optimal delivery of compounds directly to the ischemic region.

* Corresponding author at: Center for Advanced Translational Stroke Science, Department of Neurosurgery, University of Kentucky, 741 S. Limestone, BBSRB-B375, Lexington, KY 40536-0230, USA.
E-mail address: jill.roberts@uky.edu (J.M. Roberts).

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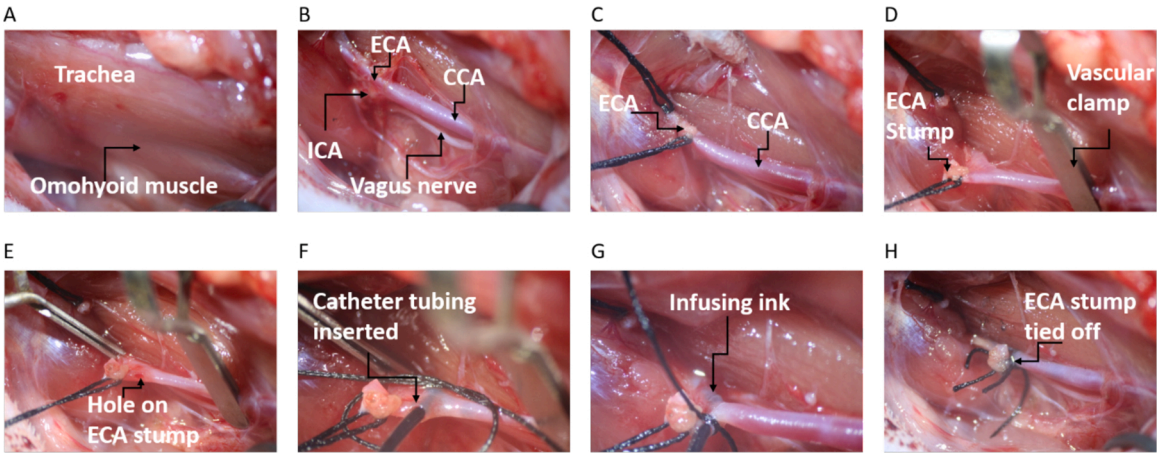

Fig. 1. Representative images of the surgical area in the rat. (**A**) Visualization of the location of the trachea and the Omohyoid muscle (which is cut and removed to access the CCA). (**B**) The CCA, the ECA/ICA bifurcation off the CCA, and the vagus nerve separated after the carotid sheath was removed. (**C**) The distal and proximal suture ties on the ECA. (**D**) Formation of the ECA stump after cutting between the distal and proximal suture ties, and a vascular clamp added to the CCA. (**E**) Creation of a hole on the ECA stump where the catheter tubing is inserted, following the addition of a vascular clamp on the ICA. (**F**) Catheter tubing inserted into the ECA stump, and advanced to the start of the ICA. (**G**) Infusion of the ink into the ICA. (**H**) The ECA has been tied off after removal of the tubing.

2. Materials and methods

2.1. Materials

A 15 cm length of Micro-renathane implantation tubing (0.025" x 0.012"; Braintree Scientific, MRE025) was used for delivery of compounds into the external carotid artery (ECA), through the ICA, and to the brain. A 30 G removable needle (0.5" with point 3 tip; Hamilton Syringe Co, #7803-07) was attached to the tubing and screwed onto a 100 µl Hamilton gas tight syringe (Hamilton Syringe Co. 7656-01), which was then placed into a syringe pump (Braintree Scientific, BS-8000). Two vascular clamps (Micro-serrines, FST-18055-01) were used for the occlusion of the common carotid artery (CCA) and ICA. Three, 9 cm sections of 5-0 silk suture was used to tie off the proximal and distal portions of the ECA, and for securing the implantation tubing into the ECA.

2.2. Animal and surgical preparation

The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of Kentucky and experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. This study used Sprague Dawley rats (Envigo; approximately 4 months old) with an N = 21 males (n = 3/injection rate) weighing between 380−500 g with a mean of 415 g, and an N = 23 females (n = 3−4/injection rate) weighing between 220−350 g with a mean of 264 g. As this was an exploratory study rather than a confirmatory study, power calculations were not used, and smaller groups sizes were favored. All rats were housed in a climate-controlled room on a 14/10 h light/dark cycle and food and water were provided *ad libitum*. Pre-op analgesic (Carprofen 50 mg/mL, diluted with saline to 5 mg/mL; dosed at 5 mg/kg s.c.) and Atropine (0.54 mg/mL, diluted with saline to 0.108 mg/mL; dosed at 0.04 mg/kg s.c.) was given subcutaneously based on body weight. Rats were placed in an induction chamber and anesthetized using 5% isoflurane with 1 L of oxygen. The cervical neck region was shaved from the mandible to the top of the sternum, and cleaned with Hibiclens (chlorhexidine scrub) prior to 70 % EtOH and then a betadine solution. Anesthesia was maintained with a nosecone that received 2.5 % Isoflurane with 1 L of oxygen. Since our laboratory will eventually combine the IA procedure with the MCAO stroke surgery, these rats did not receive any heat support during the procedure, as heat increases mortality in our stroked rats.

2.3. Isolation of the CCA and ECA/ICA bifurcation

A midline (vertical) neck incision was performed and the salivary glands were separated to visualize the trachea. The sternocleidomastoid muscle (SCM), located adjacent to the trachea, and was pulled away from the target area using lone star hooks. The planar omohyoid muscle covering the carotid sheath/artery was blunt dissected (Fig. 1A) and fat and connective tissue was removed to expose the CCA and vagus nerve, which were carefully separated. This continued anteriorly to isolate the internal carotid (ICA)/external carotid (ECA) arteries. (Fig. 1B) The superior thyroid artery (STA), the first collateral of the ECA, and the occipital artery (OA), was isolated and cauterized using fine-tipped curved forceps and a low-temp cautery.

2.4. Creating the ECA Stump for tubing insertion

Two 9-inch segments of 5−0 silk suture were placed underneath the ECA. One suture was tied to ligate the ECA as far distal as possible from the ECA/ICA bifurcation, and the second was tied just proximal to the first, leaving enough space to cut between them, forming a stump (Fig. 1C). The proximal suture that held the ECA stump was taped down, providing tension when inserting the catheter tubing. Of note, creating the ECA stump is not necessary if you are not combining the intra-arterial injection with a middle cerebral artery occlusion (MCAO) surgery. By cutting the ECA in half and creating a stump, it allows for easier insertion of a MCAO filament into the brain for occlusion.

2.5. Injection procedure

2.5.1. Carbon black ink and syringe prep

A mixture of fountain inks (Pelikan-Fount India and Higgins Fountain Pen India) in a 1:9 ratio was prepared fresh as previously described (Maniskas, Bix et al. 2015). We chose this mixture due to its low viscosity and ability to permanently stain large and small vessels equally as previously published (Hasan, Herz et al. 2012). A 15 cm length of Micro-Renathane catheter tubing was attached to a 30 G removable needle by using fine tipped forceps under a dissecting microscope, with approximately 3−4 mm of tubing placed onto the needle. We made a 45 degree angle cut on the opposite end of the tubing for easier vessel insertion. The ink was loaded into the 100 µL Hamilton gas tight syringe at a downward 45 degree angle to prevent air bubbles from forming within the syringe. The needle with tubing was attached to the syringe and the tubing was primed with ink to remove air.

Table 1
IA injection rates in naive male and female rats.

Male Rats	Injection Rate (μl/min)	Injection Volume (μl)	Hemisphere Staining Ipsilateral	Contralateral
(N = 21 rats)	3	25	No	No
3 rats/rate	3.5	25	No	No
	4	**25**	**Yes**	**No**
	4.5	**25**	**Yes**	**No**
	5	**25**	**Yes**	**No**
	6	**25**	**Yes**	**No**
	7	25	Yes	Yes
Female Rats	**Injection Rate (μl/min)**	**Injection Volume (μl)**	**Hemisphere Staining Ipsilateral**	**Contralateral**
(N = 23 rats)	**2**	**25**	**Yes**	**No**
3–4 rats/rate	**2.5**	**25**	**Yes**	**No**
	3	**25**	**Yes**	**No**
	3.5	**25**	**Yes**	**No**
	4	**25**	**Yes**	**No**
	4.5	25	Yes	Yes
	5	25	Yes	Yes

2.5.2. Micro-angio tubing insertion into ECA

Vascular clamps were placed onto the CCA and ICA. A small hole was made in the ECA stump using micro-scissors, being sure not to create a hole too close to the bifurcation. A small amount of blood loss occurs when you have successfully made a hole, but excessive bleeding is an indication that either the CCA or ICA are not sufficiently clamped (Fig. 1D-E). The prepared catheter tubing was placed into the ECA hole that was created and advanced to the start of the ICA within the bifurcation (Fig. 1F), which was best done with the use of fine tipped forceps 0.5 cm from the tip of the tubing and tension on the proximal suture holding the ECA stump. A third piece of 9 inch, 5–0 silk suture was placed around the ECA and catheter tubing, to temporarily anchor the tubing, and form a tight seal around the vessel wall. The vascular clamp was then removed from the ICA, then the CCA, establishing reperfusion.

2.5.3. Ink injection flow rate and volume

After 5 min of reperfusion, 25 μL of ink was injected at flow rates of 2.5 μL, 3 μL, 3.5 μL, 4 μL, 4.5 μL, 5 μL, 6 μL, and 7 μL per minute for the male rats. The female rats were injected at flow rates of 2 μL, 2.5 μL, 3 μL, 3.5 μL, 4 μL, 4.5 μL, and 5 μL per minute. (Fig. 1G).

2.5.4. Removal of catheter tubing

The catheter tubing was removed by placing vascular clamps back on

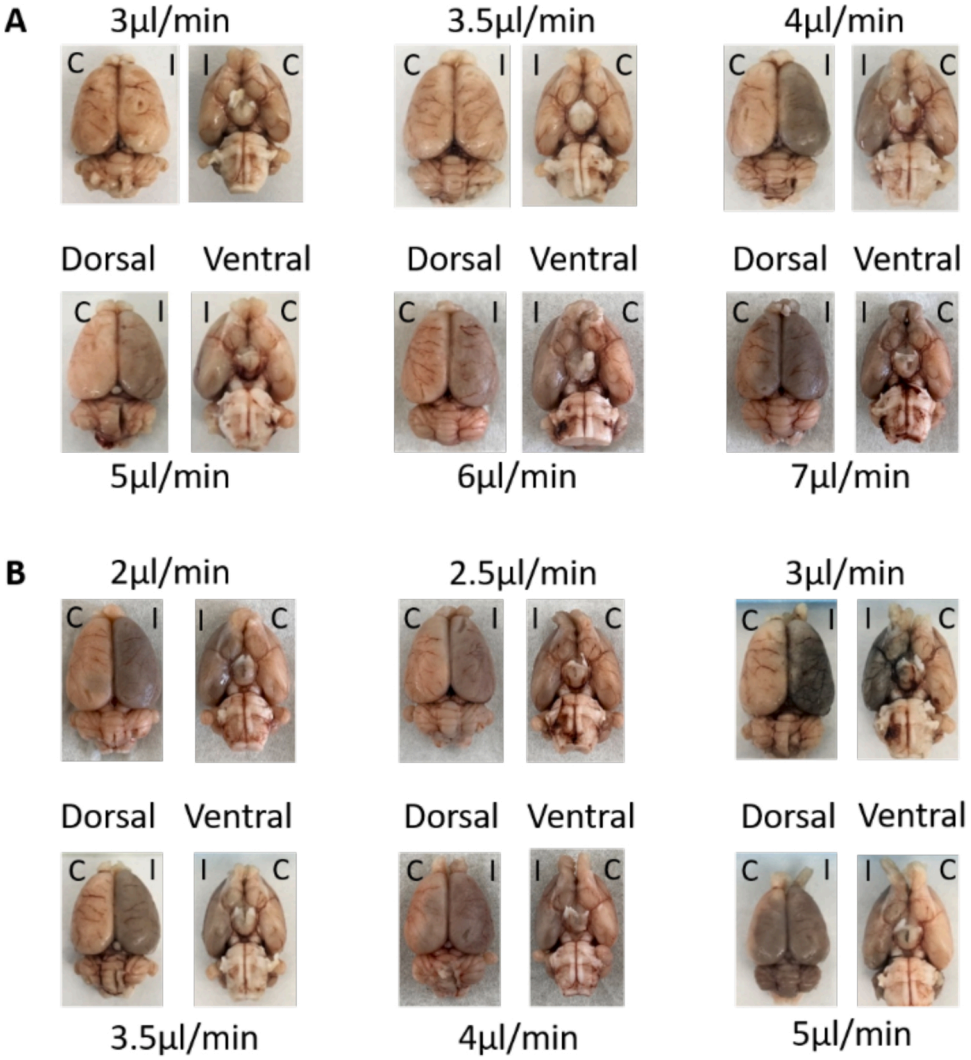

Fig. 2. (**A**) Male rat brains stained with ink following IA injections at injection rates of 3 μL/min, 3.5 μL/min, 4 μL/min, 5 μL/min, 6 μL/min, and 7 μL/min. (**B**) Female rat brains stained with ink following IA injections at injection rates of 2 μL/min, 2.5 μL/min, 3 μL/min, 3.5 μL/min, 4 μL/min, and 5 μL/min. **I**: Ipsilateral hemisphere, **C**: Contralateral hemisphere. The dark area is the ink that has entered the brain.

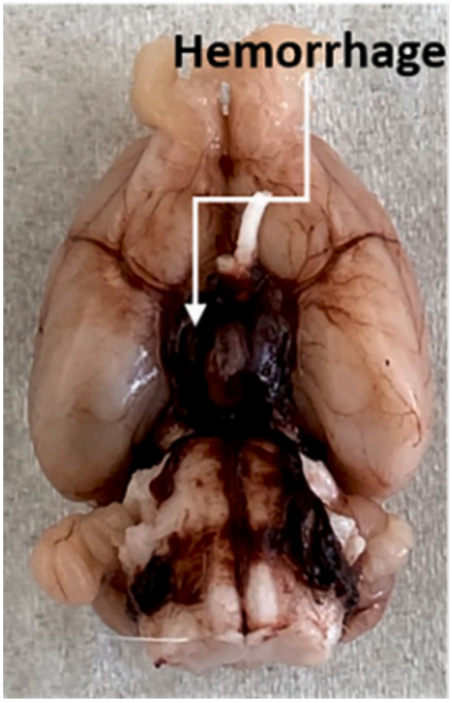

Fig. 3. Ventral brain region of a male rat with an IA infusion of ink at 7 μL/min, producing the formation of a subarachnoid hemorrhage.

the CCA and the ICA. The tubing was slowly pulled back until completely removed from the ECA stump. The suture was tightened to tie off the ECA vessel completely. The vascular clamps were removed from the ICA and CCA to establish reperfusion (Fig. 1H). Vessels were reperfused for 5 min prior to euthanasia to assess the infusion of ink.

2.6. Flow optimization

Our stated goal was to optimize infusion conditions. An optimized injection would infuse the ink into the ipsilateral MCA territory, with minimal cross penetration into the contralateral hemisphere or posterior circulation. In addition, optimal technique would not result in any complication such as hemorrhage.

3. Results

3.1. Flow rate and injection volume

The flow rates and volume used are based on previously reported data in mice (Maniskas, Bix et al. 2015). Male rats weighing between 380−500 g received an IA injection of carbon black ink (25 μL) at 2.5 μL, 3 μL, 3.5 μL, 4 μL, 4.5 μL, 5 μL, 6 μL or 7 μL per minute (Table 1). Injection rates of 4−6 μl/min among the male rats showed optimal IA infusion of ink in the ipsilateral hemisphere, with minimal staining in the contralateral hemisphere and no presence of hemorrhage (Fig. 2A). The 2.5 μL/min rate was not strong enough to overcome the blood flow at the CCA bifurcation in the male rats, and the ink backfilled into the catheter tubing. Rates of 3–3.5 μl/min in male rats took thirty seconds to one minute before ink entered into the ICA, and no staining in the ipsilateral hemisphere was observed. A rate of 7 μL/min resulted in contralateral staining (n = 1) (Fig. 2A) and a subarachnoid hemorrhage (SAH) (n = 2) (Fig. 3). Female rats weighing between 220−350 g received an IA injection of carbon black ink (25 μL) at 2 μL, 2.5 μL, 3 μL, 3.5 μL, 4 μL, 4.5 μL, and 5 μL per minute (Table 1). Injection rates of 2−4 μl/min among the female rats showed optimal IA infusion of ink in the ipsilateral hemisphere, with minimal staining in the contralateral hemisphere and no presence of hemorrhage (Figs. 2B and 4). An injection rate of 2 μL/min in the female rats showed only ipsilateral staining, but took approximately one minute for the ink to overcome the blood flow. Injection rates of 4.5−5 μl/min in the female rats resulted in contralateral staining.

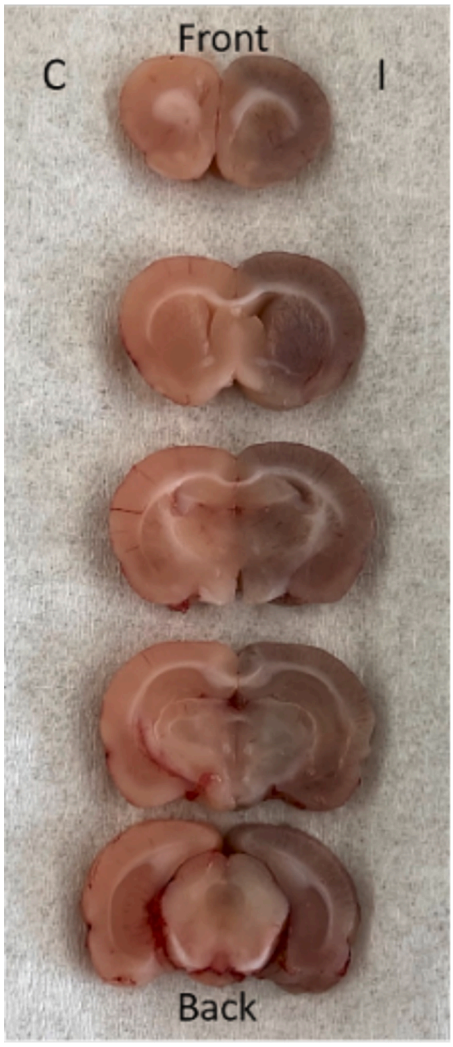

Fig. 4. Image of 2 mm brain slices of a female rat with an IA infusion of ink at 3.5 μL/min rate, with a volume of 25 μL. **I:** Ipsilateral hemisphere, **C:** Contralateral hemisphere.

4. Discussion

The endovascular thrombectomy procedure has become a standard treatment protocol for stroke patients. One advantage of this procedure is the ability to administer compounds directly to the sight of injury, bypassing initial systemic circulation. This IA method is now being utilized in preclinical studies for targeted delivery of compounds (Jovin, Albers et al. 2016). Following the Stroke Therapy Academic Industry Roundtable (STAIR) recommendation for stroke studies (Fisher, Feuerstein et al. 2009; Savitz, Baron et al. 2019), we aimed to perform IA injections in male and female rats. When determining optimal IA injection rates through the ICA, we had to consider that there would be differences between the males and females. Males were twice the size of the females at the same age, and our results prove that male rats do require a higher infusion rate. The total volume injected was 25 μL, based on work that was previously done in mice (Maniskas, Bix et al. 2015), and worked well in rats, as it stained the entire ipsilateral hemisphere (Fig. 4). Injection rates of 4−6 μl/min among the male rats

showed optimal IA infusion of ink into the ipsilateral hemisphere, with minimal staining in the contralateral hemisphere, and without any presence of a SAH. The lower rate of 2.5 μL/min did not produce enough force to overcome the male rats' blood pressure within the CCA, as the blood would backfill the catheter tubing and clot. The rates of 3–3.5 μl/min took at least one minute to overcome the male rats' blood pressure before entering into the ICA, and resulted in no ink staining in the brain. The 7 μL/min infusion rate in the male rats resulted in a SAH (Fig. 3) and contralateral staining (Fig. 2A). On the other hand, rates of 2−4 μl/min among the female rats showed optimal IA infusion of ink in the ipsilateral hemisphere, with minimal staining in the contralateral hemisphere, and without any presence of a subarachnoid hemorrhage. Infusion rates higher than 4 μL/min in the female rats induced ink staining in the contralateral hemisphere (Fig. 2B). It is important to note that at the 2 μL/min rate in the females took approximately one minute for the ink to enter into the ICA, but did result in staining the ipsilateral hemisphere. Our focus was on a targeted delivery to the ipsilateral hemisphere, with minimal ink crossing over into the contralateral hemisphere. We also wanted to prevent any unnecessary side effects that resulted in the formation of a subarachnoid or petechial hemorrhage, as that would confound results from an ischemic stroke in future studies.

A potential limitation of this study is the use of ink, as we do not know the chemical composition of the ink and it may be denser than compounds used in future IA injection studies. However, this combination of ink has been previously evaluated for the visualization of cerebral blood vessels in mice, and it is reported the two inks are very low viscosity (1.1 mPa/s and 10–50 mPa/s) and the combination at a 1:9 ratio leads to reproducible results with permanent staining through large and small vessels (Hasan, Herz et al. 2012). Our ongoing studies in stroke have found the rates do translate to our clinically relevant drugs. Additionally, following the Maniskas et al. publication that described the rates/volumes for IA injection of ink in mice, the group published several other studies using clinically relevant compounds (*e.g.*, verapamil, nitroglycerin) at the same rate/volume (Maniskas, Roberts et al. 2016; Fraser, Maniskas et al. 2017). Since rats are commonly used in preclinical studies, and rates of infusion are not previously reported, we optimized the IA procedure for rats. We recommend a range of infusion rates since the weight of male and female rats at the same age is highly varied, and plays a large role in the optimal rate. Future studies that utilize the IA injection method may be needed to optimize the rate of infusion based on the compound used and the weight or age of the animal.

One advantage of IA injection through the ICA is the reduced systemic circulation prior to reaching the target brain tissue (Arnberg, Samen et al. 2014). Not only is IA injection making great strides in the field of stroke research, it is also now being utilized in other fields such as cancer studies (Joshi, Cooke et al. 2017), (Huang, Boltze et al. 2020), CNS studies, testing the effects of steroids on rats (Dawley, Moeller-Bertram et al. 2009) and traumatic brain injuries (Osanai, Kuroda et al. 2012). The method is being adapted for larger animals, including canines and rabbits (Srinivasan, Gumin et al. 2020), (Lundberg, Jussing et al. 2017), as there is great value in the use of large animal models of disease for increased translation to humans (Boltze, Modo et al. 2019; Herrmann, Meckel et al. 2019). A proof-of-concept study performed in rabbits showed IA injections are safe and feasible in large animals. Importantly, rabbits treated with tumor infiltrating lymphocytes (TIL) *via* the IA route showed that more cells reached the desired target or tumor compared to IV infusions (Lundberg, Jussing et al. 2017).

Mouse MCAO occlusion studies with IA injections have shown that ligating the pterygopalatine artery (PPA; branch off the ICA) prior to injection, maximizes the amount of solution that travels up to the ischemic region (Guo, Ge et al. 2013). In our studies, some animals showed ink had entered into the PPA and stained the muscle tissue, but the amount was minimal. Ligating the PPA is considered unnecessary for the MCAO occlusion model, and due to its technical difficulties and possible complications, few studies utilize this technique (Guo, Ge et al. 2013; Azedi, Mehrpour et al. 2019). In turn, we also found that it wasn't necessary to ligate the PPA as targeted delivery to the brain was achieved.

In conclusion, the adoption of IA administration of compounds allows for targeted delivery to the brain and having a better understanding of the effects of sex and/or weight on the infusion rate will help to develop specific treatments for stroke or other diseases (Haast, Gustafson et al. 2012). This translational animal model combined with the MCAO model will provide a paradigm to develop adjuvant therapeutics for both male and female patients.

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Author contributions

Sarah Messmer: Data curation, formal analysis, methodology, writing-original draft.

Justin Fraser: Conceptualization, writing-review and editing.

Keith Pennypacker: Conceptualization, funding acquisition, writing-review and editing.

Jill Roberts: Conceptualization, supervision, writing-review and editing.

Declaration of Competing Interest

The authors have no competing interests to declare.

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