Comparison of middle cerebral artery occlusion models conducted by Koizumi and Longa methods: A systematic review and meta-analysis of rodent data

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Abstract

Ischemic stroke in rodents is usually induced by intraluminal middle cerebral artery occlusion (MCAO) via common carotid artery (CCA) plugging filament invented by Koizumi et al (MCAO-KM), or external carotid artery (CCA) plugging filament created by Longa et al (MCAO-LG). To date, a systematic comparison between the two methods remains missing. Here, we performed a meta-analysis in terms of model establishment, cerebral blood flow (CBF), and cerebral ischemia-reperfusion injury (CIRI) between of them. Literature mining suggests that MCAO-KM brings shorter operation time \((p = 0.007)\), higher probability of plugging filament \((p < 0.001)\) and molding establishment \((p = 0.006)\), lower possibility of subarachnoid hemorrhage (SAH) \((p = 0.02)\), larger infarct volume \((p = 0.003)\), and severer brain edema \((p = 0.002)\) and neurological deficit \((p = 0.03)\). Nevertheless, MCAO-LG shows more adequate CBF after ischemia-reperfusion \((p < 0.001)\), higher model survival rate \((p = 0.02)\), and greater infarct rate \((p = 0.007)\).

In conclusion, the MCAO-KM method is simple to operate with high modeling success rate, and it is suitable for the study of brain edema under long-term hypoperfusion, the MCAO-LG method is highly challenging for novices, and it is suitable for the study of CIRI caused by acute ischemia-reperfusion. These findings are expected to benefit in the selection of intraluminal filament MCAO models prior to undertaking ischemic stroke preclinical effectiveness trials.

1. Introduction

Stroke is one of the leading causes of death and long-term disability across the world, and a reliable ischemia stroke model is essential to produce an effective therapy for the destructive cerebrovascular accident[1–3]. The MCAO model conducted by intraluminal filament is considered as the most clinically relevant surgical model to mimic human ischemic stroke with advantage of minor craniotomy trauma, stable controllability of reperfusion, and high reproducibility, etc[4, 5]. This model was first reported by Koizumig in 1986[6], and modified by Longa in 1989[7], it have produced a profound influence on the research of ischemic stroke.

The main differences between Koizumig's method (MCAO-KM) and Longa's method (MCAO-LG) reside in the route of filament insertion to the cerebral artery and, subsequently, the CBF resupply mode as well as degree of reperfusion. Specifically, for MCAO-LG, the occlusion of middle cerebral artery (MCA) by filament is accomplished via inserting the external carotid artery (ECA), and the ischemic tissue is reperfused by bilateral common carotid arteries (CCA). But, for MCAO-KM, the filament blocked MCA is achieved by plugging through the CCA, and the reperfusion is accomplished via contralateral CCA by means of Willis ring (Fig. 1a).

The intraluminal filament model is applicable to the study of preclinical neuroprotective drugs. Some scholars have conducted comparative studies on the two methods, but the results of previous studies were rooted in a relatively small sample size, and there is no relevant meta-analysis to systematically compare their distinctions. Methodically reviewing and meta-analysis of all relevant studies in an objective and quantitative manner provide us with much credible and solid evidence to demonstrate the
unique characteristics of each method. Therefore, in this study, we conducted a meta-analysis to determine the distinctions of modeling establishment and brain injury (Fig. 1b) between the two methods, aiming to provide reference for practitioners in this field.

2. Methods

2.1 Search strategy and study inclusion

The review was registered on the PROSPERO database prior to initiation (registration number CRD42022331652). A comprehensive search strategy was conducted in Web of Science, PubMed, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database from their inceptions to July 2022 with the search terms: (Longa's method OR external carotid artery insertion OR bilateral common carotid reperfusion) AND (Koizumi's method OR common carotid artery insertion OR unilateral common carotid reperfusion) AND (intraluminal filament model OR middle cerebral artery occlusion OR focal cerebral ischemia).

We included articles if (1) animal models: MCAO model was built by intraluminal filament method, without restriction of ischemia and reperfusion duration; (2) interventions: the route of filament into the brain (common carotid artery insertion and external carotid artery insertion), or a surgical method (Koizumi’s method and Longa’s method), or a reperfusion mode (bilateral common carotid reperfusion or unilateral common carotid reperfusion); (3) Outcomes: operation duration, inserting filament success rate, probability of SAH, model animal mortality rate and modeling success rate, cerebral infarction size, brain edema rate, neurological deficit score.

2.2 Data Extraction and quality assessment

Two independent reviewers assessed related articles for the eligibility, and extracted the following details: (1) document elements: first author and year of publication; (2) animal datas: strains, sex, and weight (or age); (3) surgical details: anesthetic, ischemia duration, and reperfusion duration; (4) experimental outcomes: mean value, standard deviation, and sample size. WebPlotDigitizer (Version 4.4. 2020) was used for data extrapolation from graphs of published articles. In addition, any divergences were resolved by a senior author.

Quality of evidence in included studies was conducted based on a ten-item modified scale[9, 10]: (a) peer reviewed publication; (b) random allocation; (c) control of physiological parameter; (d) blinded conduct of the experiments; (e) blinded assessment of outcome; (f) use of anesthetic without significant neuroprotective activity; (g) complications in animals (aged, diabetic and hypertensive etc.); (h) sample size calculation; (i) compliance with animal welfare regulations; (j) statement of potential conflict of interests.

2.3 Statistical analysis
RevMan (version 5.4) was used for meta-analysis. Relative risk (RR) was estimated for all dichotomous variables. The weighted mean differences (WMD or MD) was calculated as a summary statistic if the continuous-type variable outcomes adopted the same scale, and the standardized mean difference (SMD) was used if the indexes were measured by various methods or techniques. Heterogeneity between studies was assessed via a standard chi-square test and $I^2$ statistic, $p \geq 0.01$, $I^2 \leq 50\%$ and $p < 0.01$, $I^2 > 50\%$ are considered low and high heterogeneity, respectively. If no statistical evidence of heterogeneity existed, the fixed effect (FE) model was performed with 95% confidence interval (CI); if statistical heterogeneity was found, the sensitivity analysis and subgroup analysis were used. Statistically significance for all analyses were considered if $p < 0.05$. Egger’s tests were employed to detect publication bias, which was completed by Stata (version 15.1).

3. Results

3.1 Study search and selection

After initial search from four English databases (Web of Science and PubMed) and Chinese databases (CNKI and Wanfang), a total of 142 potentially eligible studies were identified, and 61 studies were ruled out due to duplication and irrelevance. Further, thirty-nine studies were excluded owing to invalid records, and 14 studies were removed from the remaining 42 full-text articles post careful investigation. Ultimately, a total of 28 studies were included in the systematic mete-analysis. The flowchart of literature search is provided in the Supplement 1.

3.2 Study Characteristics

All the experimental animals were male-dominated rodents, except for one study sexes in half. Isoflurane were frequently used as anesthetics, others, including ketamine, pentobarbital sodium and fentanyl, etc. The treatment and plugging depth of the filament were reported in almost all literature. Cerebral ischemic injury in the included studies was induced by transient MCAO (tMCAO) or permanent MCAO (pMCAO). The characteristics of the included studies are provided in the Supplement 2.

The comparison of model establishment, CBF and ischemic brain injury were the focus of our study. Among them, the success rate of plugging filament, incidence of SAH, model mortality rate and model success rate were analyzed as dichotomous variables. While, the surgical operation duration, cerebral infarction size, brain edema rate and neurological deficit score were analyzed as continuous variables. The calculation formula of relevant indicators are shown in Supplement 3.

3.3 Quality of Included Studies

Study quality scores for 28 studies counted in this meta-analysis were summarized in Table 1. The quality scores varied from 3 to 8 with the average as 5.46. All the studies were peer-reviewed publications. Twenty-four studies declared randomization of group allocation, and 21 studies described the monitoring of physiological parameters. Besides, one study masked the details of experimental designs, and 14
studies reported blinded assessment of outcome. Thirteen studies avoided the use of anesthetics with marked neuroprotective properties. None of the studies reported the application of co-morbidities in animals. Twenty-five studies reported sample size calculation. Among all of them, 18 studies stated the compliance with animal welfare regulations, and 9 studies addressed the conflict of interests (Table 1).
Table 1
Quality evaluation of included studies.

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Study quality items are A, Peer-reviewed publication; B, Random grouping; C, Monitoring of physiological parameters (eg. temperature, blood pressure, gases); D, Blinded conduct of ischemia; E, Blinded assessment of outcomes; F, Use of anesthetic without marked intrinsic neuroprotective properties (eg, isoflurane, ketamine, halothane ); G, Animal with co-morbidities (eg., diabetic, aged, or hypertensive); H, Sample size calculation; I, Statement of compliance with animal welfare regulations; J, Statement of potential conflict of interests.

3.4 Comparisons between the two methods in the model preparation

3.4.1 Distinction on operation duration

Four studies[19, 27, 28, 32] reported the duration of surgical operation, and one[28] was excluded due to absence of extractable date. Overall, the operation duration of MCAO-KM was significantly shorter than that of MCAO-LG (MD=−10.72, 95% CI [−18.58, −2.86], p = 0.007, heterogeneity I² = 98%, p < 0.00001) (Fig. 2a). The separation and ligation of the pterygopalatine artery (PPA) as well as the surgical proficiency may be important sources of heterogeneity. Of note, the study[28] also point out that the operation time of MCAO-KM was shorter than MCAO-LG methods, which consistent with the pooled MD estimation.

3.4.2 Distinction on probability of plugging filament

The success rates of filament insertion were reported in three studies[11, 22, 27]. Overall, the MCAO-KM shows a higher probability of plugging filament than MCAO-LG (RR = 1.43, 95% CI [1.20, 1.70], p < 0.0001, heterogeneity I² = 84%, p = 0.002) (Supplement 4), and one study [27] should be the source of heterogeneity through sensitivity analyses. After removal of this study, the pooled result between the two methods remained similar and the heterogeneity was decreased (RR = 1.59, 95% CI [1.30, 1.96], p < 0.00001, heterogeneity I² = 0%, p = 0.53) (Fig. 2b).

3.4.3 Distinction on postoperative mortality

Nineteen studies[14, 18−24, 27−32, 34−38] reported the rodent mortality after plugging filament, and one study[37] was excluded due to lack of extractable data. Overall, and, no significant difference between two methods was observed (RR = 1.09, 95% CI [0.86, 1.38], P = 0.47, heterogeneity I² = 21%, P = 0.20) (Fig. 3). Of note, sub-analyses show that model animals produced by MCAO-KM exhibited higher mortality than that by MCAO-LG in the tMCAO subgroup (RR = 1.44, 95%CI [1.07, 1.95], p = 0.02, heterogeneity I² = 0%, p = 0.73), whereas, the opposite result was found in the pMCAO subgroup (RR = 0.66, 95%CI [0.45, 0.96], p = 0.03, heterogeneity I² = 32%, p = 0.20). The p-value of Egger's regression test in the tMCAO subgroup was 0.291, indicating no significant publication bias (Supplement 5).

3.4.4 Distinction on occurrence of SAH
Nine studies [18, 19, 21, 24–27, 31, 38] reported the occurrence of SAH after operation, and one study [26] was excluded due to lack of detailed data. Overall, the meta-analysis results indicate that the modeling method of MCAO-KM causes a lower probability of SAH compared to the MCAO-LG with no substantial heterogeneity (RR = 0.43, 95% CI [0.20, 0.90], p = 0.02, heterogeneity $I^2 = 0\%$, $p = 0.96$) (Fig. 4).

### 3.4.5 Distinction on success rate of MCAO models

The success rates of MCAO models were assessed in 16 studies [12, 18–28, 30, 34–36]. Overall, the MCAO-KM brings statistically higher probability on model success than the MCAO-LG (RR = 1.14, 95% CI [1.03, 1.27], $p = 0.01$, heterogeneity $I^2 = 45\%$, $p = 0.02$). Subgroup analyses suggest that the MCAO-KM supports higher model success rate in the pMCAO subgroup (RR = 1.34, 95% CI [1.09, 1.66], $p = 0.006$, heterogeneity $I^2 = 0\%$, $p = 0.51$), but not tMCAO (RR = 1.06, 95% CI [0.94, 1.20], $p = 0.33$, heterogeneity $I^2 = 46\%$, $p = 0.04$) (Supplement 6a).

Sensitivity analysis of the tMCAO subgroups revealed one study [25] may be the source of heterogeneity. After deletion of this study, no significant difference between the two methods was found in overall effect (RR = 1.08, 95% CI [0.97, 1.20], $p = 0.14$, heterogeneity $I^2 = 24\%$, $p = 0.17$) as well as tMCAO subgroup (RR = 0.97, 95% CI [0.86, 1.10], $p = 0.64$, heterogeneity $I^2 = 0\%$, $p = 0.53$). However, the MCAO-KM method's success rate remains higher in the pMCAO subgroup (Fig. 5). The $p$-value of Egger's regression test in the tMCAO subgroup was 0.089, indicating no significant publication bias (Supplement 6b & 6c).

### 3.5 Comparisons between the two methods in CBF and brain injury

#### 3.5.1 Distinction on CBF after ischemia or ischemia-reperfusion

Eight studies [13, 16, 28, 29, 32, 33, 37, 38] with 9 comparisons were applied to evaluate CBF after cerebral ischemia or ischemia-reperfusion between MCAO-KM and MCAO-LG, and one study [32] was excluded due to lack of sample size, and another study [16] was also excluded because it did not reperfused by removing the filament. Overall, there was no significant difference in CBF between the two methods during ischemia (SMD = 0.18; 95% CI [-0.32, 0.68], $p = 0.48$; heterogeneity $I^2 = 40\%$, $p = 0.14$) (Fig. 6a). Interestingly, after reperfusion, the CBF achieved by MCAO-KM was dramatically lower than that by MCAO-LG (SMD=-1.34; 95% CI [-1.85, -0.83], $p < 0.00001$; heterogeneity $I^2 = 60\%$, $p = 0.02$) (Supplement 7). After exclusion of one study [38] as a potential source of heterogeneity, the CBF outcomes between the two methods remained similar and the heterogeneity was significantly reduced (SMD=-1.12; 95% CI[-1.65, -0.59], $p < 0.0001$; heterogeneity $I^2 = 11\%$, $p = 0.35$) (Fig. 6b).

#### 3.5.2 Distinction on cerebral infarction size

Eleven studies [13, 15, 19, 21, 27–29, 31, 34, 35, 39] evaluated the cerebral infarction rates between MCAO-KM and MCAO-LG methods (Supplement 8 & Supplement 9), and one study [34] was excluded due
to lack of sample size. Overall, the cerebral infarction rates of the MCAO-KM was markedly lower than the MCAO-LG (MD=-3.37; 95% CI[-4.71, -2.04], p < 0.00001; heterogeneity I^2 = 82%, p < 0.00001) (Supplement 8a). Sub-analyses suggest that the MCAO-KM gets a low cerebral infarction rates in tMCAO subgroup, but not in pMCAO subgroup (MD=-3.53, 95% CI [-4.91, -2.15], p < 0.00001, heterogeneity I^2 = 84%, p < 0.00001; and MD=-1.12; 95% CI [-6.37, 4.14], p = 0.68 heterogeneity I^2 = 0%, p = 0.95, respectively) (Supplement 8a). After removal of one study[29], the distinction of cerebral infarction rates remained significant between the two methods, and the heterogeneity of overall effect as well as tMCAO subgroup was eliminated (SMD=-2.10, 95% CI [-3.63, -0.57], p = 0.007, heterogeneity I^2 = 39%, p = 0.10 in tMCAO subgroup; and SMD=-2.02, 95% CI [-3.49, -0.56], p = 0.007, heterogeneity I^2 = 26%, p = 0.18 in overall effect) (Fig. 7a). The p-value of Egger's regression test in the tMCAO subgroup was 0.390, verifying no significant publication bias (Supplement 8b & 8c).

Twelve studies [13, 14, 16–18, 20, 24, 30, 32, 33, 37, 38] evaluated the distinction of cerebral lesion volumes between the two modeling methods (Supplement 10 & Supplement 11). Meta-analysis suggests that the average cerebral lesion volumes of the MCAO-KM rodents was higher than the MCAO-LG rodents (SMD = 0.68; 95% CI [0.46, 0.91], p < 0.00001; heterogeneity I^2 = 59%, p = 0.003) (Supplement 10a). Sub-analyses suggest that the MCAO-KM animals show a higher average cerebral infarction volume than MCAO-LG in both tMCAO and pMCAO subgroups (SMD = 0.61; 95% CI [0.36, 0.86], p < 0.00001; heterogeneity I^2 = 57%, p = 0.003; and SMD = 0.96, 95% CI [0.47, 1.45], p = 0.0001, heterogeneity I^2 = 66%, p = 0.001, respectively) (Supplement 10a). Sensitivity analyses pointed out that two studies [30, 38] should be the source of heterogeneity. After removing these studies, the heterogeneity was significantly reduced. Sub-analyses suggest that the MCAO-KM animals showed a higher average cerebral lesion volume in tMCAO but not pMCAO subgroup (SMD = 0.54; 95% CI [0.28, 0.80], p < 0.00001, heterogeneity I^2 = 0%, p = 0.84 in tMCAO; SMD = 0.57, 95% CI [0.00, 1.13], p = 0.05, heterogeneity I^2 = 39%, p = 0.16 in pMCAO; and SMD = 0.54, 95% CI [0.31, 0.78], p < 0.00001, heterogeneity I^2 = 0%, p = 0.67 in overall effect) (Fig. 7b). The p-value of Egger's regression test in the tMCAO subgroup was 0.679, indicating no significant publication bias (Supplement 10b & 10c).

3.5.3 Distinction on brain edema

The assessments of the brain edema rates were performed in six studies[12, 16, 24, 26, 34, 38], and two studies [26, 34] were excluded due to lack of detailed data (Supplement 12). Overall, the MCAO-KM animals produced severer brain edema compared to the MCAO-LG with marked heterogeneity (SMD = 0.53, 95% CI [0.03, 1.02], p = 0.04, heterogeneity I^2 = 71%, p = 0.005) (Supplement 12). Subgroup analysis indicates that significant differences occurs in the tMCAO but not in the pMCAO subgroup (SMD = 0.70, 95% CI [0.12, 1.28], p = 0.02, heterogeneity I^2 = 78%, p = 0.003, and SMD = 0.10, 95% CI [-0.82, 1.02], p = 0.83, heterogeneity I^2 = 51%, p = 0.15, respectively). Sensitivity analysis uncovered that one study[38] is a potential source of heterogeneity. After removal of this study, the pooled estimation of brain edema between the two MCAO animals remained similar and the heterogeneity was eliminated (SMD = 0.93, 95% CI [0.34, 1.53], p = 0.002, heterogeneity I^2 = 0%, p = 0.88 in tMCAO subgroup; SMD = 0.10, 95% CI [-0.82, 0.00].
1.02], \( p = 0.83 \), heterogeneity \( I^2 = 51\% \), \( p = 0.15 \) in pMCAO subgroup; and SMD = 0.68, 95% CI [0.18, 1.18], \( p = 0.007 \), heterogeneity \( I^2 = 12\% \), \( p = 0.34 \) in overall effect) (Fig. 8).

### 3.5.4 Distinctions on neurological deficit scores

Nineteen studies evaluated neurological deficits via Longa score[13, 16, 19, 22, 25, 26, 30–32, 34, 36], Bederson score[24, 35], modified neurological severity scores (mNSS) score[17, 29, 37], and Garcia score[24, 27, 38] (Supplement 13). Among them, three articles [16, 26, 32] were excluded due to absence of available data. Of note, the higher the Garcia score, the better the neurobehavior, which is contrary to other scoring methods, thus, these studies using Garcia score were not pooled into the sub-analysis (Supplement 14). Overall, the average neurological deficit scores of the MCAO-KM animals significantly higher than that of MCAO-LG animals without heterogeneity (SMD = 0.21, 95% CI [0.02, 0.39], \( p = 0.03 \), heterogeneity \( I^2 = 20\% \), \( p = 0.21 \) (Fig. 9).

### 4. Discussion

Stroke accounts for 11.1% of global deaths and remains a worldwide health burden [40]. About 87% of strokes in humans are ischemic strokes, and 70% of cerebral infarcts are caused by occlusion of the MCA and its branches[41]. The MCAO-KM and MCAO-LG modeling methods are the two most common ways of achieving MCAO as classical surgical approaches in preclinical experiments, and they are invaluable for researchers to understand stroke pathophysiology and develop new therapeutics. However, in preclinical studies, the two classic intraluminal filament approaches for MCAO are considered alternatives, and some researchers even believed that they are interchangeable [24, 31]. Therefore, it is critical to distinguish between them in order to develop an appropriate stroke model.

#### 4.1 Distinctions in model establishment

The fundamental distinction between the MCAO-KM and MCAO-LG methods is the surgical procedure's complexity. Because most anesthetics have neuroprotective benefits against ischemic stroke, the prolonged duration of anesthesia may impact the therapeutic effect of candidate medications [42]. According to our experience, the MCAO-KM is easier to perform because it does not require ligating the ECA and its embranchment prior to ischemia, which shortens operation time (Fig. 2a) and may decrease eating difficulties caused by injuries of soft tissues and cranial nerves [43]. Furthermore, CCA is easier to plug a filament than ECA because the former is thicker and straighter than the latter (Fig. 2b), which explains the reason why MCAO-KM shows higher success rate of insertion filament and shorter operation time than MCAO-LG.

SAH is one of the leading causes of postoperative mortality in intraluminal filament MCAO model, usually caused by excessive insertion of the filament [44]. Generally, the optimal insertion depth depends on the species, and the propulsion of the thread stops when the finger feels a slight resistance after it enters the intracranial cavity [29, 32]. Arterioles derive from the ECA are prone to bleeding, thus, the slipknots around ECA need to be tied more tightly (Fig. 1a), which results in a reduced perception of protraction resistance
by the fingers. It may be a direct factor causing elevated SAH in MCAO-LG animals with a higher risk of intracranial vascular puncture (Fig. 4).

Low mortality is advantageous, representing an improved model of MCAO, allowing reduced number of rodents to be used to meet the research goal. There was no overall difference in model mortality between the two surgical methods, but the distinct results were found in the subgroup analyses (Fig. 3). In the tMCAO subgroup, the animal mortality of the MCAO-KM was higher than MCAO-LG (Fig. 3a), which may be related to the long-term hypoperfusion of the ischemic hemisphere caused by permanent ligation of CCA [29]. Conversely, in the pMCAO subgroup, the higher mortality occurs in MCAO-LG (Fig. 3b), which may be interpreted by the greater surgical damage caused by a relatively complex procedure.

Model success rate, as a comprehensive index, reflects the difficulty of operation. For the tMCAO model, there is no significant difference between the two methods (Fig. 5a), however, for the pMCAO model, the success rate of MCAO-KM is higher than MCAO-LG (Fig. 5b). Given the foregoing, it is reasonable to believe that the MCAO-KM method is simple to model establishment. In other words, the MCAO-LG method is challenging for a fledgling.

### 4.2 Distinctions in CBF

The mode and extent of reperfusion are the main distinctions between the two methods in physio-pathology. In short, the MCAO-LG animals' reperfusion is mainly derived from bilateral CCA, whereas the MCAO-KM animals' reperfusion is primarily derived from contralateral CCA via Willis ring because the ipsilateral CCA was permanently ligated (Fig. 1a). After plugging in the filament, CBF detection revealed that no significant difference between the two groups (Fig. 6a), and the decline was about 60% of the pre-ischemia level [16, 18]. Interestingly, reperfusion in MCAO-KM animals reached only 50% of baseline levels, while, in MCAO-LG rodents, reperfusion could rapidly restore to near-normal levels (Fig. 6b). Furthermore, high-resolution MR angiography defines the MCAO-KM as a ischemia-reperfusion model with chronic hypoperfusion, whereas the MCAO-LG method achieves ischemia complete reperfusion [38].

Surge reperfusion observed with removal of the filament may be like that observed with clinical endovascular thrombectomy[45]. Considering the insufficient reperfusion of MCAO-KM animals, some scholars believe that the MCAO-LG method with complete reperfusion should be given priority in the exploration of the neuroprotective agents on cerebral ischemia-reperfusion injury [45]. In fact, only 7–10% patients in developed countries receive effective thrombolytic therapy within the treatment time window [46, 47]. What's worse, stroke patients - approximately 30.9–72.3% - do not achieve full revascularization despite receiving thrombolytic therapy [48–50]. Besides, the researchers observed that the brain would provide hypoperfusion blood to the infarcted core via collateral vessels in humans or rodents that did not receive recanalization treatment [51, 52]. Thus, stroke patients with chronic hypoperfusion injury was more common than that of complete reperfusion [53]. In other words, although the ischemia stroke model prepared by the MCAO-KM method does not achieve complete reperfusion, it may be closes to the main situation of no or incomplete thrombolysis.
4.3 Distinctions in cerebral infarction size, brain edema rate and neurological deficit score

We evaluated the infarction size in forms of volume and percentage, and interestingly, the results from the two versions were polar opposites (Fig. 7). As is well known, full ischemia-reperfusion rapidly mobilizes amounts of erythrocytes and hemoglobin [54], and mitochondrial dysfunction causes the oxygen transported by this hemoglobin to be converted into amounts of reactive oxygen species [55, 56]. Additionally, via interacting with endothelial cells, a considerable number of circulating immune cells enter the brain parenchyma after ischemia-reperfusion [57]. All of the aforementioned factors lead to untimely oxidative stress and inflammatory reactions, which result in secondary CIRI. Another investigation discovered that rats that received quick flow restoration had more infarctions than those who underwent incremental flow restoration [58]. Thus, it is speculated that the bigger cerebral infarction in the MGO-LG rodents is caused by the more severe CIRI produced by the remarkable recovery of CBF.

Ligation of a unilateral CCA significantly destroys the blood-brain barrier and increases brain water content in rats [59], Similar to this, individuals who have failed recanalization experience an increase and expansion of the edema volume [60]. Therefore, it may be reasonable to assume that the permanent closure of CCA following filament removal explains why the MCAO-KM technique results in more severe brain edema (Fig. 8). Giving that edema-corrected infarction progression is greater than the edema progression, the level of edema is insufficient to account for the overall expansion of infarction volume [60]. When estimating how an intervention would affect infarct size, a modified formula rather than pure infarction volume must be used since the peak of cerebral edema, which happens after 2 to 3 days, should be taken into account as for calculating the infarction volume [61].

Neurological abnormalities and cognitive deterioration are linked to chronic cerebral hypoperfusion. In this study, we discovered that neurological impairments in MCAO-KM rodents were more severe as a result of the protracted hypoperfusion brought on by unilateral CCA ligation (Fig. 9). Important to keep in mind is that the impact of permanent CCA blockage on cognitive function may negate the effectiveness of emerging treatment options that aim to treat stroke-induced vascular dementia or stroke with Alzheimer's disease[37].

4.4 Distinctions in inflammation

The development of ischemia disease is heavily influenced by inflammation, and the inflammatory response brought on by various surgical techniques is time-dependent. As early as 4–6 hours after surgery, neutrophils were observed in the ischemic core following ischemia [62, 63]. The interaction between leukocytes and endothelial cells was studied by Smith H K et al [29], who discovered that both animals' ischemic brain tissue was filled with a significant number of rolling leukocytes. Interestingly, cells remaining stationary within the vessel only occurred in MCAO-LG after urgent reperfusion. Another study [34] discovered that NF-κB expression in the ischemic core was considerably greater in the MCAO-LG than the MCAO-KM after 24 hours of reperfusion. However, during the subacute stage of ischemic
stroke, Onufriev et colleagues [35] discovered that IL-1 together with corticosterone discharge and amass in the MCAO-KM rat hippocampus, indicating that MCAO-KM predisposes the animals to corticosterone-dependent distant neuroinflammatory hippocampal injury. Furthermore, in terms of long-term inflammatory responses, Yang et al [37] found no significant difference between the two modeling approaches in astrocyte and microglial activation, as well as apoptotic neuronal death. Thus, MCAO-LG may have a greater inflammatory response in the acute phase, whereas MCAO-KM may have a stronger inflammatory response in the subacute period.

4.5 Distinctions in other aspects

Mice's pterygopalatine artery, the first internal carotid artery branch, is the source of the ocular artery [38]. The majority of retinal reactions to ischemia coincide with brain tissue in MCAO-KM animals, with substantial atrophy of the inner retinal layers due to permanent CCA ligation, whereas MCAO-LG mice revealed no serious histological retinal abnormalities [38]. Thus, the MCAO-KM was created to better study the pathophysiology of cerebral combine retinal ischemia.

5. Conclusion

Based on the meta-analysis results, we conclude that the surgical procedure - MCAO-KM or MCAO-LG - should not be chosen arbitrarily, and the filament insertion route has a substantial effect on model establishment, CBF, and CIRI.

In summary, MCAO-KM has advantages in model establishment, such as shorter operation time, easier filament insertion, lower risk of SAH, and higher model success rate; it is more appropriate for the study of ischemia-induced brain edema due to chronic hypo-reperfusion with a higher risk of death and severe neurological deficits. However, MCAO-LG is better suited for the study of acute CIRI due to its ability to preserve CCA integrity with a sophisticated and challenging surgical procedure, it has a low model mortality, high CBF replenishment, large cerebral infarction, and an acute inflammatory response.

Instead of arbitrary variables, this discovery may provide scientists with actual parameters for selecting a suitable intraluminal filament MCAO model.

Abbreviations

BBB, blood-brain barrier; CBF, cerebral blood flow; CCA, common carotid artery; CIRI: cerebral ischemia-reperfusion injury; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; MCAO, middle cerebral artery occlusion; mNSS, modified neurological severity scores; pMCAO, permanent middle cerebral artery occlusion; PPA, pterodylopalatal artery; SAH, subarachnoid hemorrhage; tMCAO, transient middle cerebral artery occlusion.

Declarations
Acknowledgements

We appreciate all researchers, some because their literature was included in our meta-analysis, and others because they were involved in this work.

Ethical Approval

This research does not require an ethics approval since no experiments with human participants or animal samples were contained as part of the review.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Authors' contributions

Yong Li, Bowen Deng, Xianzhi Huang and Lin Liu of our team are responsible for collecting relevant documents, Yong Li and Liying He are responsible for writing the first draft of this paper, Sijing Liu, Li Tan, and Caixia Yang are responsible for reviewing the manuscript, and Yong Li is responsible for submitting the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary materials.

Supplementary Information

The online version contains supplementary material available at https://

References


18. Cam E, Kilic E, Yulug B, Ritz MF. Occlusion of the Middle Cerebral Artery in Rats; 2008. 52-65 p.


**Figures**
Figure 1

(a) Diagram of the intraluminal filament model made by Koizumi's method and Longa's method[8].
ECA=external carotid artery, CCA=common carotid artery, MCA=middle cerebral artery, ICA=internal carotid artery, ACA=anterior cerebral artery, PCA=posterior cerebral arteries, PPA=pterygopalatine artery, OA=ophthalmic artery, ST=superior thyroid artery; (b) Diagram of the experimental animal whereabouts. The blue and red boxes represent model preparation and brain injury indicators, respectively.
Figure 2

Comparison of (a) operation duration and (b) success rate of filament insertion between the MCAO-KM and MCAO-LG
Figure 3

Comparison of postoperative mortality between MCAO-KM and MCAO-LG

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MCAO-KM Events</th>
<th>Total</th>
<th>MCAO-LG Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
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<td>Cam Erтгұл 2008</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>9.5%</td>
<td>0.60 [0.06, 4.47]</td>
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<td>10</td>
<td>3</td>
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<td>16.7%</td>
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<tr>
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<td>15</td>
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<td>6</td>
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<td>Yang Zanjiang 2008</td>
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<td>25</td>
<td>4</td>
<td>25</td>
<td>19.0%</td>
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<td>25</td>
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<td>1.00 [0.07, 15.12]</td>
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<td>129</td>
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<td>0.43 [0.20, 0.90]</td>
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<td>19</td>
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</table>

Heterogeneity: Chi² = 1.90, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.02)

Figure 4
Comparison of postoperative SAH between MCAO-KM and MCAO-LG

Figure 5

Comparison of modeling success rates between MCAO-KM and MCAO-LG
Comparison of CBF between MCAO-KM and MCAO-LG after (a) cerebral ischemia and (b) ischemia-reperfusion
Figure 7

Comparison of cerebral infarction size between MCAO-KM and MCAO-LG split by (a) infarction rate and (b) lesion volume
### Figure 8

Comparison of brain edema in rodents between MCAO-KM and MCAO-LG

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MCAO-KM</th>
<th>MCAO-LG</th>
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<td>Mean</td>
<td>SD</td>
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<td>70.16</td>
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<td>89.23</td>
<td>52.32</td>
<td>9</td>
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<tr>
<td>Qu Qiumin 2000</td>
<td>52.37</td>
<td>1.28</td>
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<td>50.9</td>
<td>0.96</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>27</strong></td>
<td><strong>37</strong></td>
<td><strong>23</strong></td>
<td><strong>70.2%</strong></td>
<td></td>
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<tr>
<td><strong>Heterogeneity:</strong> Chi² = 0.26, df = 2 (P = 0.88); I² = 0% Test for overall effect: Z = 3.06 (P = 0.002)</td>
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<th>MCAO-LG</th>
<th>Std. Mean Difference</th>
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<td><strong>10</strong></td>
<td><strong>33</strong></td>
<td><strong>10</strong></td>
<td><strong>29.8%</strong></td>
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**Total (95% CI):** 37 | 33 | 100.0% | 0.68 [0.18, 1.18] |

**Test for subgroup differences:** Chi² = 2.23, df = 1 (P = 0.14), I² = 55.2%

### Figure 9

Comparison of brain edema in rodents between MCAO-KM and MCAO-LG

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<th>Study or Subgroup</th>
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<th>MCAO-LG</th>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td><strong>134</strong></td>
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<td><strong>Heterogeneity:</strong> Chi² = 17.69, df = 9 (P = 0.04); I² = 49% Test for overall effect: Z = 2.01 (P = 0.04)</td>
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<table>
<thead>
<tr>
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<th>MCAO-LG</th>
<th>Std. Mean Difference</th>
<th>IV. Fixed, 95% CI</th>
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<td>2.18</td>
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<td><strong>31</strong></td>
<td><strong>12.2%</strong></td>
<td><strong>0.40 [-0.13, 0.94]</strong></td>
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</table>

**Total (95% CI):** 233 | 237 | 100.0% | 0.21 [0.02, 0.39] |

**Heterogeneity:** Chi² = 21.31, df = 17 (P = 0.021); I² = 20% Test for overall effect: Z = 2.17 (P = 0.03) Test for subgroup differences: Chi² = 1.59, df = 2 (P = 0.45), I² = 0%
Comparison of neurological deficit score between MCAO-KM and MCAO-LG

Supplementary Files

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- SupplementalMaterial.docx