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Systematic review of survival time in experimental mouse stroke with impact on reliability of infarct estimation

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HIGHLIGHTS

- A common method is proposed for infarct size estimation of experimental mice stroke.
- Longer survival times are recommended to avoid the peak time of edema formation.
- Pro and cons of translational issues in experimental mice stroke are discussed.

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ABSTRACT

Background: Stroke is the second most common cause of death worldwide. Only one treatment for acute ischemic stroke is currently available, thrombolysis with rt-PA, but it is limited in its use. Many efforts have been invested in order to find additive treatments, without success.

A multitude of reasons for the translational problems from mouse experimental stroke to clinical trials probably exists, including infarct size estimations around the peak time of edema formation. Furthermore, edema is a more prominent feature of stroke in mice than in humans, because of the tendency to produce larger infarcts with more substantial edema.

Purpose: This paper will give an overview of previous studies of experimental mouse stroke, and correlate survival time to peak time of edema formation. Furthermore, investigations of whether the included studies corrected the infarct measurements for edema and a comparison of correction methods will be discussed.

Method: Relevant terms were searched in the National Library of Medicine PubMed database. A method for classification of infarct measurement methods was made using a naming convention.

Conclusion: Our study shows that infarct size estimations are often performed around the peak time of edema, with a median of 24 h. Most studies do consider edema formation, however, there is no consensus on what method to use to correct for edema. Furthermore, investigations into neuroprotective drugs should use longer survival times to ensure completion of the investigated process. Our findings indicate a need for more research in this area, and establishment of common correction methodology.

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1. Introduction

Stroke is the second most common cause of death worldwide (Casals et al., 2014). 85% of the cases are ischemic (Hjerteforeningen, 2014), caused by a decrease in cerebral blood flow (CBF) from a thrombus or an embolus. Within minutes, neurons in the central core of the insult die. The tissue surrounding the central core, the penumbra – where CBF levels may fall under a functional threshold – remains viable and thus salvageable (Akpan et al., 2011).

Only one treatment for acute ischemic stroke is registered and approved by the FDA—thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) (Liu and McCullough, 2011). As few as 13–19% of all stroke patients are treated with rt-PA due to its many limitations (Dansk, 2013) including a narrow time window, contraindications, and complications (Dansk, 2013). Furthermore, only between 10 and 30% of the treated patients experience better outcomes compared to no treatment (Hjerteforeningen, 2014).

Thus, there is an urgent need for an additive treatment to rt-PA. However, despite more than thousands of experimental treatments and papers on the subject (Ginsberg, 2007; O'Collins et al., 2006), no clinically effective neuroprotective agent has been found. It is peculiar why so many preclinical trials have demonstrated promising significant protection against ischemic cell death, whereas virtually none of it can be reproduced in clinical trials. The question of whether stroke models really model stroke (Mergenthaler and Meisel, 2012) has been raised in numerous publications (Casals et al., 2014; Mergenthaler and Meisel, 2012; Braeuninger and Kleinschnitz, 2009; Carmichael, 2005), and recommendations to overcome the translational problems have been proposed in the STAIR criteria (Fisher et al., 2009).

The most used experimental model of focal ischemia involves middle cerebral artery occlusion (MCAO) in rodents (Carmichael, 2005). This model is considered equivalent to focal cerebral infarction in man (Barone et al., 1993). Infarct size is often used to evaluate the therapeutic effects of potential neuroprotectants (Carmichael, 2005). Therefore, it is of utmost importance to have an exact and reproducible method for estimating infarct size.

In this study, we focus on mouse MCAO as a model for ischemic stroke, since many researchers use transgenic mice for stroke research (Casals et al., 2014). However, a major problem inherent in this model, is enlargement of the infarcted tissue caused by edema (Park and Kang, 2000). Human strokes are divided into nonmalignant and malignant infarctions. Substantial progressive edema is observed in malignant infarctions, which occur when the infarct is greater than 39% of the ipsilateral hemisphere (Carmichael, 2005). In experimental mouse stroke, most strokes are 21–45% of the ipsilateral hemisphere, whereas in humans most strokes are in the range of 4,5–14% of the ipsilateral hemisphere (Carmichael, 2005). Thus, edema is a more prominent feature of stroke in the mouse than in humans, because of the tendency to produce larger infarcts with more substantial edema. Therefore, it might be speculated that malignant infarctions are overrepresented compared to nonmalignant infarctions in the mouse model. Thus, the effect of an investigated drug might be over- or underestimated because of this.

Ischemic brain edema is a pathological accumulation of fluid in the intracellular and extracellular spaces of the brain due to a combination of cytotoxic and vasogenic edema (Fishman, 1992). The vasogenic edema is caused by a shifting of fluid from the vasculature to the extracellular spaces of the brain by disruption of the blood brain barrier, which develops over hours to days (Fishman, 1992; Rubin, 2011). The cytotoxic edema is swelling of cells in the brain due to failure of ATP-dependent ion transporters in neuronal, glial and endothelial cells due to the ischemic insult (Kahle et al., 2009). As sodium builds up in the cells, water enters to restore osmotic equilibrium. This cytotoxic response develops within minutes after ischemia (Fishman, 1992). Due to edema in the ischemic area, total ipsilateral hemisphere volume will increase. Peak time of cerebral edema is 1–3 days (Park and Kang, 2000; Col and Jha, 2003). Thus, estimation of infarct size is influenced by edema especially in the first days after an insult, which can lead to errors in stroke volume determinations (Swanson et al., 1990; Lin et al., 1993).

There are many reasons why it is important to correct for edema in experimental mouse stroke. First, there are differences in edema formation in individual mice and between different mouse strains, which can make it difficult to compare infarct volume results if not adjusted for edema (Barone et al., 1993). Also, therapeutics that directly reduces edema can lead to the disbelieve that the actual infarct size has decreased—this effect of the drug might lead to better outcomes in mice but not in humans due to differences

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