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COMMENTARY

Animal Models for the Study of Subarachnoid Hemorrhage: Are We Moving Towards Increased Standardization?

Serge Marbacher [1,2]

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The discussion on the need for more standardized experimental subarachnoid hemorrhage (SAH) models was initiated at the 12th International Conference on Neurovascular Events after Subarachnoid Hemorrhage in Lucerne, Switzerland (July 2013) during a workshop session entitled "Animal Models for the Study of Delayed Cerebral Vasospasm (DCVS) and Early Brain Injury (EBI) after SAH". The SAH research community shared experiences and discussed current practices and future prospects of SAH animal models [1].

As a follow-up to the collegial and cooperative initial discussions, *Translational Stroke Research* has offered to publish a series of critical reviews of established and novel SAH models in mice, rats, rabbits, dogs, and nonhuman primates [2–8]. These reviews address important aspects regarding parameters used, advantages and limitations, outcome measures and applicability for the study of DCVS and EBI and are meant to provide guidance on how to conduct experiments in the future.

More recently, preliminary results of a systematic literature review on in vivo animal SAH studies presented at the 13th International Conference on Neurovascular Events after Subarachnoid Hemorrhage in Karuizawa, Japan (September 2015) revealed that the focus of preclinical research efforts shifted significantly from DCVS towards the study of EBI [9]. The number of preclinical SAH studies unrelated to DCVS has increased steadily over the past years with currently more than twice as many addressing EBI rather than DCVS. At the same time, the variety of species and SAH models has been reduced to only a few techniques which are mainly applied in mice, rats, and rabbits. Traditional large animal models for the study of DCVS after SAH (such as the dog double injection or the primate blot clot model) are hardly used anymore.

Despite the reduction in SAH animal models, the arbitrary use of important parameters associated with experimental SAH has not decreased when compared with earlier data [10]. For example, in the past 10 years, more than 15 different fixed or weight-adapted blood volumes (0.3–1.5 ml/kg) have been injected, either manually or pump assisted, with or without withdrawal of cerebrospinal fluid and with various injection times (10–300 s) in single or double injection of cisterna magna model in rabbits. The variability of these important parameters is not limited to the well-known SAH technique of cisterna magna injection in rats and rabbits. Significant differences have also been reported for the relatively newly introduced mice species. Injected blood volumes (30–100 μl) as well as injection times (10–120 s) in the pre-chiasmatic injection model vary greatly. In the endovascular perforation technique, variously sized (4–0, 5–0, and 6–0), blunted, and sharpened filaments cause a wide range in SAH severity in terms of SAH volume and ICP increase.

The lack of adequate and standardized SAH animal models is one reason for the disappointing translation of basic research into a clinically effective treatment. Continuing efforts to promote awareness of the importance of more standardized use of parameters associated with SAH animal models is urgently needed. As a next step, we plan to use the CAMARADES collaborative approach to systematically review and meta-analyze the animals used in experimental studies (http://www.dcn.ed.ac.uk/camarades). The aim is to establish a dataset of experimental studies using SAH models in order to identify the most commonly applied and reliable parameters as a basis for discussion. The ultimate aim is to seek consensus on standards that would increase

✉ Serge Marbacher
serge.marbacher@ksa.ch

[1] Kantonsspital Aarau, Aarau, Switzerland

[2] University of Bern, Bern, Switzerland

comparison of data between different laboratories, ultimately optimizing both animal welfare and scientific validity.

Compliance with Ethical Standards

Conflict of Interest None.

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