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Efficacy of bumetanide in animal models of ischemic stroke: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 March 2024 and was last updated on 07 March 2024.

INTRODUCTION

Review question / Objective This meta-analysis aimed to describe the efficacy of bumetanide in improving infarct volume, brain edema, and behavioral outcomes in animal models of ischemia stroke.

Condition being studied Ischemic stroke, defined as a clinical syndrome of sudden central nervous system dysfunction, seriously threatens human life and imposes a great mental and economic burden on society, families, and individuals With the increase in the population of older adults in China, stroke-induced disability continues to increase and is the leading cause of death; therefore, developing new stroke treatment methods, including neuroprotective strategies . Although more than 700 drugs have been described for experimental stroke, only tissue-type plasminogen activators have been shown to be effective in human studies [3, 4]. These disadvantages include the risk of bleeding, short effective time window, and unsuitability for many patients [5]. Therefore, it is necessary to investigate other drugs for treating ischemic stroke.

METHODS

Search strategy We selected relevant studies from publications in PubMed, Embase and Web of Science from their inception to February 2024. The search terms used were (stroke OR cerebrovascular OR cerebral infarct OR ischemia OR middle cerebral artery OR middle cerebral artery occlusion) AND (rodent OR mouse OR rat) AND (bumetanide OR NKCC1). The language of the publications was limited to English. Two investigators (Jiadi Hou and Haichun Xu) independently retrieved the literature. Disputes that

arose during the selection process were discussed and resolved by both the parties.

Participant or population Permanent or transient middle cerebral artery occlusion (pMCAO or tMCAO), ET-1 stroke model, or other focal stroke models were performed on rodents.

Intervention Animals treated with bumetanide.

Comparator Our study aimed to systematically determine the efficacy of bumetanide in reducing infarct volume, cerebral edema, and neurological function in rodent models of ischemic stroke and to observe the neuroprotective effects of bumetanide in stroke model and duration subgroups.

Study designs to be included experimental studies were presented in the original research articles.

Eligibility criteria Permanent or transient middle cerebral artery occlusion (pMCAO or tMCAO), ET-1 stroke model, or other focal stroke models were performed on rodents; 2) a control group was set up with a placebo; 3) adequate data on functional outcomes or infarction volume were provided; and 4) experimental studies were presented in the original research articles.

Information sources We selected relevant studies from publications in PubMed, Embase and Web of Science from their inception to February 2024.

Main outcome(s) We conclude that bumetanide appears to be effective in reducing infarct volume and brain edema and improving behavioral recovery in animal models of cerebral ischemia. This mechanism needs to be confirmed through further investigation.

Quality assessment / Risk of bias analysis (1) Peer review publication. (2) Strength-response relationship; (3) Random assignment study; (4) Blinded treatment administration; (5) Blind evaluation of results; (6) Physiological parameters monitoring; (7) Sample size calculation; (8) ≥2 outcome parameters were evaluated; (9) Avoidance of anesthetics with marked intrinsic neuroprotective properties (ketamine); (10) Comply with animal welfare regulations; and (11) Statement of potential conflict of interest. Thus, the studies were classified into three quality categories (category I, 8–11 items; category II, 4–7 items; and category III, 0–3 items).

Strategy of data synthesis The results of the included trials were analyzed for each endpoint: infarct volume, cerebral edema, and neurological outcomes, including neurological score, memory, and limb function. All analyses were performed using STATA 15.0. The I2 statistic was used for heterogeneity assessment. When heterogeneity was strong and could not be eliminated, a random-effects model was used instead of a fixed-effects model to obtain the overall MD/SMD and 95% CI . A subgroup analysis was conducted to examine the effect of bumetanide according to the stroke model (permanent or temporary) and time point of intervention (pre-treatment or post-treatment). A leave-one-out sensitivity analysis was performed to evaluate the robustness of the results. Publication bias was checked by a funnel plot, and asymmetry was estimated by Egger's test and the trimand-fill method. If the p-value was <0.01, the significance of all the analyses was accepted.

Subgroup analysis A subgroup analysis was conducted to examine the effect of bumetanide according to the stroke model (permanent or temporary) and time point of intervention (pre-treatment or post-treatment).

Sensitivity analysis A leave-one-out sensitivity analysis was performed to evaluate the robustness of the results.

Country(ies) involved China.

Keywords Bumetanide; Infarct volume; Behavioral Recovery; Animal models of ischemia stroke; Meta-analysis.

Contributions of each author

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