Use of Batroxobin in Central and Peripheral Ischemic Vascular Diseases: A Systematic Review

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Background and Purpose: The mechanism of action of Batroxobin included the decomposition of the fibrinogen to fibrin degradation products (FDPs) and D-dimer and mobilization of endothelial cells to release endogenous nt-PA and to promote thrombolysis. This review aims to summarize current study findings about batroxobin on correcting cerebral arterial, venous, and peripheral vascular diseases, to explore the mechanism of batroxobin on anti-thrombosis process.

Methods: A thorough literature search was conducted utilizing the PubMed Central (PMC) and EMBASE databases to identify studies up to June 2021. Data from clinical studies and animal experiments about batroxobin were extracted, integrated and analyzed based on Cochrane handbook for systematic reviews of interventions approach and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), including the condition of subjects, the usage and dosage, research observation index and main findings.

Results: A total of 62 studies were enrolled in this systematic review, including 26 clinical studies and 36 animal experiments. The 26 clinical studies involved 873 patients with arterial ischemic events, 92 cases with cerebral venous thrombosis, 13 cases with cerebral cortical vein thrombosis, and 1,049 cases with peripheral vascular diseases. These patients included 452 males and 392 females aged 65.6 ± 5.53 years. The results revealed that batroxobin had broad effects, including improving clinical prognosis (n = 12), preventing thrombosis (n = 7), promoting thrombolysis (n = 6), and improving vascular cognitive dysfunction (n = 1). The effects of batroxobin on reducing neuronal apoptosis (n = 8), relieving cellular edema (n = 4), improving spatial memory (n = 3), and promoting thrombolysis (n = 13) were concluded in animal experiments. The predominant mechanisms explored in animal experiments involved promoting depolymerization of fibrinogen polymers (n = 6), regulating the expression of related molecules (n = 9); such as intercellular adhesion molecule, heat shock proteins, tumor necrosis factor), reducing oxidative stress (n = 5), and reducing inflammation response (n = 4).
Conclusion: Batroxobin can correct both arterial and venous ischemic diseases by promoting depolymerization of fibrinogen polymers, regulating the expression of related molecules, reducing oxidative stress, and reducing the inflammation response.

Keywords: Batroxobin, vascular disease, ischemic, effects, mechanism

INTRODUCTION

Batroxobin, isolated from Bothrops atrox moojeni venom, is widely used in clinical such as postoperative hemostasis of surgery because of its hemostatic effect (1–4). Batroxobin has also been investigated for the treatment of deep vein thrombosis and cerebral infarction as it promotes thrombolysis, prevents recurrence of thrombus, and provides neuroprotection (5–8). In recent years, the role of Batroxobin in cerebral venous thrombotic diseases has attracted more attention with two clinical articles proposing to study the clinical value of Batroxobin in cerebral venous thrombosis (CVT) and cerebral venous sinus thrombosis (CVST), respectively (9, 10). Batroxobin may promote venous sinus recanalization through thrombolysis, and is a potentially safe and effective adjunct therapeutic agent in patients with a high level of fibrinogen. Another small clinical study investigated the efficacy of Batroxobin in cerebral cortical vein thrombosis (CCVT). Batroxobin significantly improved the prognosis of patients with CCVT (11). All these studies prove that Batroxobin has a wide range of clinical applications. The mechanism of action of Batroxobin included the decomposition of the fibrinogen to fibrin degradation products (FDPs) and D-dimer (12, 13) and mobilization of endothelial cells to release endogenous nt-PA and to promote thrombolysis (14, 15). However, there is a lack of literature review that summarizes the clinical effects and related mechanisms of Batroxobin. Since there is a growing interest in studying Batroxobin as a treatment strategy in cerebral venous system diseases, our study aims to summarize the previous findings to provide a theoretical basis for the use of Batroxobin in cerebral venous system diseases and facilitate future research. In this study, we review previous studies investigating Batroxobin in both clinical and experimental settings and summarize the most recent findings to provide a deep understanding of Batroxobin in treating thrombotic diseases. We also discuss the potential use of Batroxobin in the treatment of cerebral venous thrombotic diseases.

METHODS

Search Strategy

A systematic review of the literature has been performed on PubMed Central (PMC) and EMBASE databases using the keywords “Batroxobin,” “animal study,” or “clinical study.” Our review includes studies published till June 2021 that investigated Batroxobin. Cochrane handbook for systematic reviews of interventions approach and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) was followed accordingly (Supplementary Table 1).

Study Selection

Clinical (prospective and retrospective) and experimental studies that evaluated the efficacy of Batroxobin were included. Studies not related to vascular system diseases and their complications were excluded. Conference abstracts, reviews, case reports, and letters were also not included in the analysis. If two or more studies had duplicate or overlapping data, then the study with the larger sample size and more detailed data was selected. Two reviewers (D-L and SY-S) independently performed the study selection and any disagreements were resolved by discussion (Figure 1).

Data Extraction

Two authors (D-L and SY-S) extracted data from the selected studies, which was evaluated by another author (BL-J). The data were further extracted and summarized as follows: the name of the first author, year of publication, country, study characteristics (sample size and research type), subject characteristics (population and animal status, comorbid status and animal model type), detailed information of Batroxobin use, primary outcome and other main findings. All disagreements were resolved by consensus.

Outcomes

The main outcomes of the clinical trials in this review were coagulation indicators, improvement of neurological function, and thrombus recanalization and recurrence. The main outcomes of animal experiments were histopathological indexes and blood factor indexes.

RESULTS

Sixty-two studies, including 26 clinical studies and 36 animal experiments, were selected for the systematic review. The specific screening process is shown in Figure 1 and detailed information about the selected studies is listed in Tables 1, 2.

Clinical Studies

Two clinical studies, including 31 and 61 subjects, evaluated the efficacy of the combination of Batroxobin and anticoagulation in cerebral venous thrombosis (CVT) and cerebral venous sinus thrombosis (CVST), respectively (9, 10). Higher recanalization rates were found in both Batroxobin groups (adjusted OR [95% CI] of 2.5 [1.1–5.0]; adjusted OR [95%CI] of 8.10 [1.61–40.7], respectively) compared with the control groups, especially in patients with high levels of fibrinogen (adjusted OR [95% CI] of 4.7 [1.4–16.7]). The results of the two studies were inconsistent in concluding whether Batroxobin improved neurological deficits. National Institute of Health Stroke Scale (NIHSS) scores significantly improved at discharge in the Batroxobin group.
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FIGURE 1 | Flow diagram of the study selection process.

[0(0, 4.25)−5(2, 11), p = 0.036] compared with the baseline in only one study (9). A clinical study with 13 patients evaluated the effectiveness of Batroxobin in acute cerebral cortical vein thrombosis (CCVT) (11). Compared with the non-Batroxobin group, the Batroxobin group achieved a significantly improved prognosis, evaluated by the global impression of change (PGIC) (p = 0.030) in patients.

Ten studies investigated the efficacy of Batroxobin in patients with acute ischemic stroke (AIS). Six studies reported significant improvement of nerve function evaluated by NIHSS (n = 1), Neurological deficit scale (NDS) (n = 2), European stroke scale (ESS) (n = 2) (16–19, 21, 22). Two studies reported a positive association between Batroxobin and prevention of recurrence of stroke (7, 16). Three studies concluded that Batroxobin significantly decreases the level of fibrinogen and increases the level of D-dimer (18, 20, 23).

One study investigated the effect of Batroxobin in improving vascular cognitive dysfunction (24). Significant differences were observed in Mini-mental state examination (MMSE) and activities of daily living (ADL) scores compared with baseline.

The application of Batroxobin was also tested in peripheral vascular disease, deep venous thrombosis (DVT) (n = 5) (5, 25–27, 64), peripheral arterial thrombosis (PAT) (n = 5) (4, 28–30, 32), trial fibrillation (AF) (n = 1) (34) and healthy subjects (n = 1) (35). In all five DVT studies, Batroxobin promoted the recanalization of thrombosis and decreased the occurrence of restenosis of PAT. Batroxobin promoted favorable clinical outcomes in patients with peripheral arteriovenous thrombosis, evaluated by ankle-brachial index (ABI). Coagulation tests with Batroxobin showed a significant decrease in FIB (5, 27, 30) and prolongation of thrombin time (TT) (35) in these studies. Batroxobin also affected other clotting indicators such as prothrombin time (PT) and activated partial thromboplastin time (APTT), but the exact role is controversial (30, 35).

Animal Experiments

In animal experiments, the main objective was to understand the central vascular damage model that is involved in acute cerebral ischemia (ACI) [n = 8; rat(n = 6) and gerbil (n = 2)], cerebral ischemia-reperfusion (IR) [n = 6; rat(n = 3) and gerbil(n = 3)], intracerebral hemorrhage (ICH) (n = 2; rat), and spinal cord injury (SCI) (n = 2; rat). Four studies also assessed the effect of Batroxobin in the rat models of anoxic damage, nigrostriatal pathway injury, demyelinating disease, and experimental autoimmune encephalomyelitis. Twelve studies showed that Batroxobin reduces neuronal apoptosis (n = 8) (8, 36–39, 41, 43, 48) and relieves cellular edema (n = 4) (14, 15, 42, 65) by promoting the expression of growth-associated protein-43 (GAP-43) (38), increasing the level of adenosine triphosphate (ATP) (8), decreasing the hydroxyl radical production (41, 44, 65), down-regulating the heat shock proteins (HSP) (49), and down-regulating complement...
| References       | Country | Population     | Study type | Sample size, age* | Gender (F/M) | Intervention and dosage                                                                 | Outcome evaluation                                                                 | Main findings                                                                 |
|------------------|---------|----------------|------------|-------------------|--------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Song et al. (11) | China | CCVT           | Case-control | C: 9 (30.4 ± 14.5) I: 4 (32.8 ± 4.0) | 8/5          | C: LMWH bridged with Warfarin I: LMWH bridged with Warfarin + Batroxobin Dosage: 10 BU followed by 5 BU every other day, iv. drip. | • PGIC  
• Time to symptom relief  
• Recanalization rate  
• Recurrence rate  
• Recanalization degree  
• NIHSS  
• mRS  
• Adverse event  
• NIHSS  
• Recanalization rate  
• Hemorrhage rate  
• TT  
• DD  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement on PGIC scores  
Decreased time to symptom relief  
Accelerated recanalization  
Decreased recurrent rate of CCVT                                                                                                                                       |
| Ding et al. (10) | China | CVT            | Case-control | C: 10 (39.2 ± 21.5) I: 21 (29.8 ± 14.5) | 16/15        | C: LMWH bridged with Warfarin I: LMWH bridged with Warfarin + Batroxobin Dosage: 10 BU followed by 5 BU every other day, iv. drip. | • Recanalization degree  
• NIHSS  
• mRS  
• Adverse event  
• NIHSS  
• Recanalization rate  
• Hemorrhage rate  
• TT  
• DD  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Increased recanalization rate  
Increased the rate of stenosis reversion  
No statistical difference on NIHSS and mRS  
Increased recanalization rate  
Improvement on NIHSS  
No increased risk of intracranial hemorrhage  
Prolongation of TT, increased DD, and decreased Fg |
| Ding et al. (11) | China | CVST           | Case-control | C: 38 (36.3 ± 15.3) I: 23 (29.8 ± 14.5) | 30/31        | C: LMWH + Batroxobin Dosage: 10 BU followed by 5 BU every other day, iv. drip. | • mRS  
• NIHSS  
• Recanalization rate  
• Hemorrhage rate  
• TT  
• DD  
• Fg  
• Reduced Fg  
• Increased DD  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Increased recanalization rate  
Decrease of NIHSS and mRS  
No increased risk of intracranial hemorrhage  
Prolongation of TT, increased DD, and decreased Fg |
| He et al. (16)   | China | AIS            | Case-control | C: 47 (55.72 ± 9.84) I: 43 (58.91 ± 11.64) | NA           | C: Aspirin + Atorvastatin + Batroxobin I: Aspirin + Atorvastatin + Batroxobin + TCD Dosage: 10 BU, iv. drip. | • Hemodynamic monitor  
• NIHSS  
• TIBI  
• BI  
• Recurrence rate  
• NDS  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement on NIHSS and BI  
Reduction of stroke recurrence rate  
Lower NDS  
Higher general effective rate  
Improvement of ESS  
Decreased Fg  
Higher effective rate |
| Wu et al. (17)   | China | AIS            | Case-control | C: 43 I: 43     | NA           | C: Batroxobin I: Batroxobin + Edaravone | • NDS  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Decreased Fg in both group  
Higher effective rate |
| Ren et al. (18)  | China | AIS            | Case-control | 50               | NA           | C: Batroxobin I: Batroxobin + Edaravone Dosage: 10 BU followed by 5 BU every other day for 4 times, iv. drip. | • ESS  
• BI  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement of ESS  
Higher effective rate |
| Hao et al. (19)  | China | AIS            | Case-control | 45               | NA           | C: Batroxobin + Normal temperature I: Batroxobin + Local mild hypothermia | • ESS  
• Effective rate  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement of ESS  
Higher effective rate |
| Wang et al. (20) | China | AIS            | Case-control | 80               | NA           | C: Batroxobin I: Batroxobin + Edaravone Dosage: 10 BU followed by 5 BU every other day for 3 times, iv. drip. | • NDS  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Decreased Fg in both group  
Higher effective rate |
| Xu et al. (7)    | China | AIS/TIA with hyperfibrinogenemia | Case-control | C: 60 (65 ± 7.3) I: 52 (66.1 ± 8) | 85/27        | C: Saline I: Batroxobin | • Recurrence rate  
• Reduction of stroke recurrence rate  
• Physical examination  
• Fg  
• DD  
• Increased DD  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement on symptoms of motor disability  
Decreased Fg  
Decreased Fg  
Increased DD |
| Gusev et al. (21)| Russia | AIS            | Case-control | C: 45 I: 45     | NA           | C: Standard therapy I: Standard therapy + Batroxobin Dosage: 10 BU followed by 5 BU every other day for 3 times, iv. drip. | • Physical examination  
• ESS  
• BI  
• Fg  
• Decreased Fg  
• Higher effective rate  
|                   |         |                |            |                   |              |                                                                                           |                                                                                   | Improvement on symptoms of motor disability  
Decreased Fg  
Increased DD |

(Continued)
| References        | Country | Population | Study type | Sample size, age* | Gender (F/M) | Intervention and dosage | Outcome evaluation | Main findings* |
|-------------------|---------|------------|------------|-------------------|--------------|-----------------------|--------------------|----------------|
| Yu et al. (22)    | China   | AIS        | Case-control | C: 108 I: 106     | NA           | C: Conventional therapy | Effective rate     | Quicker function recovery |
|                   |         |            |            |                   |              | I: Conventional therapy + Batroxobin |                    | Shorter course of the disease |
| Tanahashi et al. (23) | Japan  | AIS        | Retro      | C:8 I:8           | NA           | C: Batroxobin           | Fg                 | Decreased RBC-A |
|                   |         |            |            |                   |              | I: Batroxobin Dosage: C: 5 BU for one time, iv. drip. I: 10 BU for one time, iv. drip |                    | Decreased Fg |
| Zhai et al. (24)  | China   | VCI        | Case-control | C: 40 I: 40       | NA           | C: Aspirin Dosage: 5 BU for 4 times a week, iv. drip. | MMSE ADL | Improvement on MMSE and ADL |
|                   |         |            |            |                   |              | I: Aspirin + Batroxobin |                    |                |
| Chen et al. (25)  | China   | DVT after PCLR | Case-control | 128              | 36/92        | LMWH + Batroxobin     | Recanalization rate | Increase in DD |
|                   |         |            |            |                   |              | I: Batroxobin Dosage: 5 BU for 3 times for distal DVT and 3 to 5 times for proximal DVT, iv. drip. |                    | Increase in recanalization rate |
| Ye et al. (26)    | China   | DVT after ACLR | Retro      | 195              | 48/123       | Batroxobin Dosage: 10 BU followed by 5 BU for 3–14 days according to the DVT symptom, iv. drip. | Recanalization rate | No PE and hemorrhage |
|                   |         |            |            |                   |              | I: Batroxobin + LMWH + Aspirin |                    | Increase in recanalization rate |
| Qin et al. (6)    | China   | DVT in AIS | Case-control | C:47 (74 ± 6) I:10 (75 ± 8) | 33/24 | Batroxobin Dosage: 10 BU followed by 5 BU for 14 days, iv. drip. | Recanalization rate | No PE and hemorrhage |
|                   |         |            |            |                   |              | I: Batroxobin + LMWH |                    | Reduction of Fg level |
| Zhang et al. (5)  | China   | DVT        | Retro      | 15               | NA           | Batroxobin + LMWH + Aspirin Dosage: 10 BU followed by 5 BU for 14 days, iv. drip. | Recanalization rate | Improvement of symptoms |
|                   |         |            |            |                   |              | I: Aspirin |                    | Increased recurrence rate |
|                   |         |            |            |                   |              | I: Urokinase +LMWH Dosage: I A1:10 BU (1-day) followed by 5 BU, iv. drip |                    | Increased CD34þ/CD31þ cells |
| Wang et al. (27)  | China   | DVT        | Retro      | I A1: 25(48 ± 16) I A2: 23(49 ± 15) I B: 14(52 ± 15) I C1: 25(60 ± 15) I C2: 25(48 ± 15) I D: 15(46 ± 15) | 66/61 | I A1: Batroxobin I A2: Batroxobin I B: LMWH I C1: Batroxobin + LMWH I C2: Batroxobin + LMWH I D: Urokinase +LMWH Dosage: I A1: 10 BU (1-day) followed by 5 BU, iv. drip | Fg Complication | The combination usage of Batroxobin + LMWH achieved the best efficacy |
|                   |         |            |            |                   |              | I A2: 10 BU (1-day) followed by 5 BU, micro pump I C1: 10 BU (1-day) followed by 5 BU, iv. drip I C2: 10 BU (1-day) followed by 5 BU, micro pump |                    | The safety of Batroxobin given in micro pump was much better. |
| References                  | Country | Population | Study type          | Sample size, age* | Gender (F/M) | Intervention and dosage | Outcome evaluation                                                                 | Main findings[^#]                                |
|-----------------------------|---------|------------|---------------------|-------------------|--------------|-------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------|
| Xue et al. ([28])           | China   | Arterial angioplasty | Case-control       | C: 26 I: 26       | NA           | C: Aspirin I: Aspirin + Batroxobin Dosage: 5 BU every other day for 6 times, iv. drip. | • ABI • Restenosis rate • Decreased restenosis rate • Increased ABI |                                |
| Wang et al. ([29])          | China   | Arterial angioplasty | Case-control       | C:26 (70.92 ± 6.53) I: 26 (69.62 ± 7.75) | 24/22        | C: Aspirin I: Aspirin + Batroxobin Dosage: 5 BU every other day for 6 times, iv. drip. | • Restenosis rate • Clinical symptom • Relief rate • Decreased restenosis rate • Increased ABI |                                |
| Yasunga et al. ([30])       | Japan   | PAT        | Retro               | 8                 | NA           | Batroxobin Dosage: 0.4–0.8 BU/kg, iv. drip. | • ABI • Decreased restenosis rate • Increased ABI |                                |
| Li et al. ([31])            | China   | Arterial angioplasty | Case-control       | C: 55 (70.60 ± 7.10) I: 46 (69.54 ± 6.91) | 56/45        | C: Aspirin I: Aspirin + Batroxobin Dosage: 5 BU every other day for 6 times, iv. drip. | • ABI • Decreased restenosis rate • Increased limb salvage-survival rates |                                |
| Wang et al. ([32])          | China   | Arterial angioplasty | Case-control       | C: 60 (70.7 ± 7.40) I: 51 (69.49 ± 6.93) | 64/47        | C: Aspirin I: Aspirin + Batroxobin Dosage: 5 BU every other day for 6 times, iv. drip. | • ABI • Decreased restenosis rate • Increased limb salvage-survival rates |                                |
| Xiao et al. ([33])          | China   | ACS after stenting | Case-control       | C: 20 I: 20       | NA           | C: Aspirin + Clopidogrel I: Aspirin + Clopidogrel + Batroxobin Dosage: 10 BU for one time, iv. drip. | • ABI • CRP • Decreased restenosis rate • Increased ABI • Decreased CRP • Decreased restenosis rate |                                |
| Sakamoto et al. ([34])      | Japan   | AF         | Self-control        | Group 1: 15 (66 ± 9) Group 2: 13 (68 ± 7) Group 3: 8 (74 ± 11) | 9/27         | Groups divided by grades of atrial spontaneous echo contrast Group 1: mild Group 2: moderate Group 3: severe Dosage: 0.2 BU/kg, iv. drip. | • Fg • Whole blood viscosity • Improvement on blood rheology • Decreased blood cell aggregation • Prevention of atrial thrombus formation |                                |
| Choi et al. ([35])          | Japan   | Healthy subjects | Case-control        | C: 6 (28.5 ± 7.4) I1: 6 (26.3 ± 7.5) I2: 6 (29.3 ± 6.2) I3: 6 (27.2 ± 2.9) | NA           | C: Placebo I1: Batroxobin I2: Batroxobin I3: Batroxobin Dosage: I1: 2.5 BU, iv. drip. I2: 5 BU, iv. drip. I3: 10 BU, iv. drip. | • PT • APPT • TT • Safety • No significant changes in PT or APPT occurred • A dose range of 2.5–10.0 BU/2.0 mL was well tolerated • Decreased Fg • Prolongation of TT. |                                |

[^*]: Mean ± standard deviation.
[^#]: Compared with control group.

CCVT, Cerebral cortical vein thrombosis; CVST, Cerebral venous sinus thrombosis; CVT, Cerebral venous thrombosis; DVT, Deep venous thrombosis; PCLR, Posterior cruciate ligament reconstruction; ACLR, Anterior cruciate ligament reconstruction; AIS, Acute ischemic stroke; TIA, Transient ischemic attack; VCI, Vascular cognitive impairment; ACS, Acute coronary; CABG, Coronary artery bypass graft; PUF, Posterior lumbar interbody fusion; PAT, Peripheral arterial thrombosis; AF, Atrial Fibrillation. Retro, Retrospective; C, Control; I, Intervention; LMWH, Low molecular weight heparin; BU, Batroxobin unit; iv. drip, intravenous drip; PGIC, Patient global impression of change; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; DD, D-dimer; US, Ultrasound; PE, Pulmonary embolism; RBC-A, Erythrocyte aggregability; TCD, Transcranial Doppler; TBB, Thrombolysis in brain ischemic score; BI, Barthel index; NDS, Neurological deficit scale; ESS, European stroke scale; MMSE, Mini-mental state examination; ADL, Activities of daily living; CRP, C-reactive protein; NS, Normal sodium; DM, Diabetes mellitus; ABI, Ankle-brachial index; PT, Prothrombin time; APPT, Activated partial thromboplastin time; Fg, Fibrinogen; FDP, Fibrinogen degradation product.
TABLE 2 | Application of batroxobin in animal experiments.

| References | Country | Animal model | Sample size | Intervention and dosage | Outcome evaluation | Main findings |
|------------|---------|--------------|-------------|-------------------------|--------------------|---------------|
| Li et al. (36) China ACI (Gerbil) NA Sham operation group | | | | | Histological assessment | Reduction of apoptosis of neurons |
| Hu et al. (37) China ACI (Rat) 120 C: No intervention | | | I1: Batroxobin | | Intracranial bleeding | Reduction of the cerebral infarct volume ratio. |
| | | | I2: Batroxobin | | Histological assessment Neurological function | No increased risk of intracranial hemorrhage |
| Wu et al. (38) China ACI (Rat) NA C: No intervention | | | I1: Batroxobin | | Histological assessment | |
| Wu et al. (39) China ACI (Rat) NA C: No intervention | | | I1: Batroxobin | | Cognitive function NCAM | |
| Wu et al. (40) China ACI (Rat) NA C: No intervention | | | I1: Batroxobin | | Cognitive function HSP32 HSP70 | |
| Wu et al. (41) China ACI (Rat) NA C: No intervention | | | I1: Batroxobin | | Cognitive function C-Jun | |
| Qun et al. (41) China ACI (Gerbil) NA C: No intervention | | | I1: Batroxobin Dosage: 8 BU/kg | | Histological examination Oxidative stress product | Ameliorated neurologic deficits Increased surviving numbers of pyramidal cell Reduction of hydroxyl radical production |
| Namikata et al. (42) Japan ACI (Rat) NA C: No intervention | | | I1: Batroxobin | | Histological examination Neurological function | |
| Xu et al. (43) China Cerebral IR (Gerbil) 45 Groups divided by drug use frequency | | | I1: Three times | | Histological examination | |
| Kang et al. (14) China Cerebral IR (Rat) 32 C: No intervention | | | I1: Batroxobin Dosage: 0.3 BU/kg | | TNF-α Histological examination | Inhibition of the excessive increase of TNF-α. Releaved cellular edema Reduced pyknosis of nerve cells No micro-thrombosis Increased SOD activities Reduction of the MDA content |
| Zhang et al. (44) China Cerebral IR (Gerbil) 60 Sham-operated group | | | Ischemia control group Normothermia group Hypothermia group Batroxobin group Hypothermia + Batroxobin group Dosage: 8 BU/kg | | Oxidative stress product | |
| Wu et al. (45) China Cerebral IR (Rat) 36 C: Saline | | | I1: Batroxobin | | Histological examination | Decreased apoptotic cells Relieved the neuronal damage |

(Continued)
| References          | Country | Animal model                  | Sample size | Intervention and dosage                      | Outcome evaluation                                      | Main findings                                      |
|---------------------|---------|-------------------------------|-------------|----------------------------------------------|--------------------------------------------------------|---------------------------------------------------|
| Chen et al. (8)     | China   | Cerebral IR (Gerbil)          | 32          | C: No intervention                           | • ATP levels                                           | • Decreased neuron death                           |
|                     |         |                               |             | I: Batroxobin with different dose            | • Neuron survival                                      | • Increased ATP levels in the infarcted area       |
|                     |         |                               |             |                                              | • Behavioral tests                                     | • Decreased 2,3-DHBA                               |
| Yi et al. (46)      | China   | Cerebral IR (Rat)             | NA          | C: No intervention                           | • Purine metabolites                                   | • Decreased adenosine, inosine, hypoxanthine, and xanthine in ECF |
| Qi et al. (47)      | China   | ICH (Rat)                     | NA          | Groups divided by dosage                     | • Histological examination                            | • Improvement of neuroethology scale of the rats.  |
|                     |         |                               |             | I1: Batroxobin 4 BU/kg group                 | • Oxidative stress product                            | • Relieved histiocyte edema and bleeding.          |
|                     |         |                               |             | I2: Batroxobin 8 BU/kg group                 | • Improvement on motor function                       | • Decreased water content, MDA, and free Ca2+ concentration |
|                     |         |                               |             | I2: Batroxobin 16 BU/kg group                | • Reduction of neuronal apoptosis and inflammation at the acute stage |
| Wu et al. (15)      | China   | ICH (Rat)                     | NA          | C: No intervention                           | • Histological assessment                            | • Attenuated brain edema formation in ICH rats.    |
|                     |         |                               |             | I: Batroxobin                                | • Immune factor                                        | • Down-regulated ICAM-1 in the perihematomal area.|
| Li et al. (48)      | China   | Nigrostriatal pathway injury (Rat) | 24          | C: Saline                                   | • Histological examination                            | • Down-regulated complement C3d and C9 expression in the perihematomal area. |
|                     |         |                               |             | I: Batroxobin                                | • Neurological function                                | • Improvement on motor function                    |
|                     |         |                               |             |                                              | • Immunochemistry                                      | • Reduction of neuronal apoptosis and inflammation at the acute stage |
| Liu et al. (49)     | China   | Anoxic damage (Rat)           | NA          | C: No intervention                           | • Histological assessment                            | • Neuroprotective effect on anoxic damage of hippocampal neurons. |
|                     |         |                               |             | I: Batroxobin                                | • HSP70                                                | • Down-regulated HSP70                             |
| Inoue et al. (50)   | USA     | Demyelinating disease (Rat)   | 52          | C: Saline                                   | • Clinical sign                                        | • Delayed the onset                                 |
|                     |         |                               |             | I: Batroxobin                                | • Fg deposition                                        | • Decreased the severity of the demyelinating disease |
|                     |         |                               |             | Dosage: 30 BU/kg                            | • Coagulation test                                     | • Decreased the mean clinical severity of the disease |
| Yang et al. (51)    | China   | EAE (Rat)                     | 36          | Batroxobin                                  | • Histological examination                            | • Ameliorated the clinical manifestation            |
|                     |         |                               |             | Dosage: 30 BU/kg                            | • Coagulation test                                     | • Delayed the course                                |
|                     |         |                               |             |                                              | • Histological examination                            | • Reduction of inflammation and demyelination       |
|                     |         |                               |             |                                              | • VEGF                                                 | • Decreased deposition of Fg                         |
|                     |         |                               |             |                                              | • BBB scores                                           | • No effect on plasma Fg                            |
|                     |         |                               |             |                                              | • Histological assessment                            | • Down-regulated the expression of p-Akt            |
|                     |         |                               |             |                                              | • VEGF                                                 | • Up-regulated the expression of MBP                |
|                     |         |                               |             |                                              | • Increased expression of VEGF                         | • Decreased Fg                                      |
|                     |         |                               |             |                                              | • Reduction of the number of apoptotic cells           | • In I1 group (2 BU/kg)                             |
|                     |         |                               |             |                                              | • Improvement the BBB scores                          | • Increased blood flow                              |
|                     |         |                               |             |                                              | • Decreased Fg                                         | • Increased survival rate of neurons                |
|                     |         |                               |             |                                              | • In I2 group (3 BU/kg)                                | • Reduced lesion size                              |
|                     |         |                               |             |                                              | • Alleviation of astrocyte and activation of microglial cell | • Increased functional recovery                   |

(Continued)
TABLE 2

| References | Country | Animal model | Sample size | Intervention and dosage | Outcome evaluation | Main findings |
|------------|---------|--------------|-------------|-------------------------|--------------------|---------------|
| Jiang et al. (53) | China | AMI (Dog) | 47 | C: No intervention  I: Batroxobin Dosage: 2 BU/kg | | Decreased mortality  Decreased MDA and CK/LDH  Improvement on myocardial function |
| Gao et al. (54) | China | AMI (Dog) | NA | C: No intervention  I: Batroxobin  I2: Aspirin  I3: Heparin Dosage: 2 BU/kg | | Dose-dependent increase in CBF  Decreased small coronary resistance |
| Tomaru et al. (55) | Japan | AMI(Dog) | 111 | I1: Batroxobin  I2: Aspirin  I3: Heparin Dosage: 2 BU/kg | | Restenosis rate |
| Seon et al. (56) | Korea | Femoral artery hemorrhage (Rat) | 120 | Groups divided by dosage  C: r-Batroxobin 0 BU/25 cm²  I1: r-Batroxobin 10 BU/25 cm²  I2: r-Batroxobin 25 BU/25 cm² | | Hemostatic activity  Coagulation test |
| Seon et al. (56) | Korea | Femoral artery hemorrhage (Rat) | NA | C: Collagen  I: Collagen + Batroxobin | | Hemostatic activity  More rapidly controlled excessive bleeding with r-Batroxobin  Improved the effect of other hemostatic dressing |
| You et al. (57) | Korea | Liver injury (Rat) | NA | Groups divided by dosage  C: Batroxobin 0 BU/ml  I1: Batroxobin 5 BU/ml  I2: Batroxobin 10 BU/ml | | Coagulation test |
| Tomaru et al. (58) | Japan | Hind limb artery injury (Dog) | 67 | I1: Heparin  I2: Argatroban  I3: Batroxobin Dosage: 0.05 BU/kg | | The rate of a thrombotic event  Coagulation test |
| Masuda et al. (59) | Japan | Hind limb ischemic injury (rat) | NA | C: Saline  I: Batroxobin | | Histological assessment  Blood perfusion |
| Tomaru et al. (54) | Japan | PAT (dogs) | 73 | C: Saline  I1: Heparin  I2: Argatroban  I3: Batroxobin Dosage: 0.05 BU/kg | | Coagulation test  The reduction of thrombotic stenosis |
| Tomaru et al. (55) | Japan | PAT(Rat) | 23 | C: No intervention  I1: nt-PA  I2: nt-PA + Heparin  I3: nt-PA + Batroxobin Dosage: 0.05 BU/kg | | The rate of recanalization |
| Yoshikawa et al. (60) | Japan | DIC (Rat) | 110 | C: Saline  I: Batroxobin Dosage: 200 BU/kg | | Fg  PT  APTT |
| Markwardt et al. (61) | German | DIC (Rat) | NA | C: Saline  I: Batroxobin | | Reduction of plasma Fg  Increase in Fg degradation products  Prolongation of PT and APTT  Reduction of Blood cell counts, platelet counts, and hematocrit level |
| Huang et al. (62) | China | Atherosclerosis 50 (Rabbit) | C: Saline  I: Batroxobin | | Fg  Platelet counts  Hemoglobin  Stability evaluation vascular plaque |

(Continued)
expression (15). Three experiments concluded that Batroxobin significantly improved the spatial memory and cognitive function in rats by regulating the expression of HSP32, HSP70 and neural cell adhesion molecule (NCAM) (40, 45, 66).

The peripheral vascular model included three bleeding models; the rest were all ischemic models including acute myocardial ischemia (AMI) (n = 3; dog), disseminated intravascular coagulation (DIC) (n = 2; rat), peripheral artery thrombosis/ischemic injury [n = 4; dog(n = 2) and rat (n = 2)], and atherosclerosis (n = 1; rabbit). Four experiments confirmed that Batroxobin decreased fibrinogen levels (47, 54, 60, 61). Further, Batroxobin decreased blood counts, platelet counts, and hematocrit level (60, 61). Two experiments showed that Batroxobin also promoted coagulation (57, 67). Other reports showed that Batroxobin also participated in stabilizing the atherosclerotic plaque, inhibiting human vascular smooth muscle cell migration, accelerating tissue repair, and expediting vascular regeneration (59, 62, 63).

**DISCUSSION**

Our review for the first time summarizes the clinical applications and possible mechanisms of Batroxobin by systemically reviewing current clinical and experimental studies (Figure 2).

**The Application of Batroxobin in Central Vascular Disease**

The effectiveness of Batroxobin in promoting recanalization (9, 10) and preventing recurrence (7, 16) of thrombus in all patients with ischemic disease, including cerebral venous sinus thrombosis (CVST) or acute ischemic stroke (AIS), were supported by several studies. In addition to its benefit for recanalization and secondary stroke prevention, treatment with Batroxobin also improved the neurologic deficits which secondary to CVST or AIS (1, 8, 14–16, 23, 67). A case-control study showed that Batroxobin in combination with aspirin improved vascular cognitive impairment (VCI) (24). Batroxobin did not increase the relative risk of any adverse events, including intracranial bleeding (9), compared with the control group.

In animal models of cerebral ischemia or ischemia-reperfusion, Batroxobin reduced the number of apoptotic neurons (8, 14, 36, 39, 41, 43), the degree of edema (14, 42) and the size of infarction (37–39, 42, 46) and the occurrence of micro-thrombosis (14). Batroxobin may produce these effects through a variety of pathophysiological mechanisms, including promotion of the expression of growth-associated protein-43 (GAP-43) (38), inhibition of the excessive increase of Tumor necrosis factor-alpha (TNF-α) (14), increase of the Superoxide dismutase (SOD) activities (44), reduction of oxygen-free damage (41, 44) and increase of the energy supply to the infarct area (8). Batroxobin increases the expression of neural cell adhesion molecule (NCAM) and downregulates the generations of heat shock proteins (HSP), such as HSP32 and HSP70, and c-jun, thereby, improving spatial memory disorder (40, 45, 66). In the models of intracerebral hemorrhage (ICH), Batroxobin effectively attenuated brain edema formation and decreased bleeding, possibly by decreasing the concentration of malondialdehyde (MDA) and free Ca2+, increasing the SOD activities and down-regulating the expression of Intercellular Adhesion Molecule 1 (ICAM-1) and complements, such as C3d and C9 (15, 65). Batroxobin was also effective in other animal models of central disease, including nigrostriatal pathway injury, widespread anoxic damage, demyelinating disease and spinal cord injury (SCI) (47–52). Batroxobin also attenuates the scar formation (48), display a direct neuroprotective effect on anoxic neuron (49) and delay the onset and the course of demyelinating disease; (50, 51) possible mechanisms include relieving inflammation (48, 51), decreasing the deposition of fibrin, down-regulating the expression of phospho-Akt (p-Akt), and up-regulating the expression of myelin basic protein (MBP) (51).

**The Application of Batroxobin in Peripheral Vascular Diseases**

Batroxobin treatment alone or in combination with other anticoagulant drugs could promote complete recanalization and prevent the incidence of postoperative deep venous thrombosis (DVT) without adverse events such as pulmonary embolism (PE) and hemorrhage (5, 25, 26, 64). Also, injection of Batroxobin with long-term micropump may get a better efficacy for DVT (27). Batroxobin in combination with aspirin also prevented restenosis
after arterial angioplasty which may be mediated by decreased regional inflammation (4, 28–30, 32). In patients with atrial fibrillation (AF), Batroxobin improved blood rheology, decreased blood cell aggregation, and prevented left atrial thrombus formation (34).

In peripheral vascular-related animal models, Batroxobin improved hemostasis (56, 57, 67), and prevented thrombosis (54, 58), accelerating tissue repair and vascular regeneration and stabilizing the atherosclerotic plaque (59, 62). The effect of Batroxobin on fibrinogen metabolism played an important role in ameliorating the formation of disseminated intravascular coagulation (DIC) (60, 61). As an adjunct, Batroxobin enhanced the thrombolytic effects of native tissue-type plasminogen activator (nt-PA) (55). The role of Batroxobin in inhibiting human vascular smooth muscle cell (SMC) migration may also play a clinical value in the future (63).

Cerebral Venous Sinus Thrombosis May Benefit More From Batroxobin

Timely diagnosis and treatment are essential for faster and more complete recanalization and better outcomes in patients with cerebral venous sinus thrombosis (68–70). However, the primary treatment of CVST is long-term oral anticoagulation. For acute and severe CVST, endovascular therapy is always used first (71). Whereas, venous recanalization is time consuming and there remains a risk of hemorrhagic transformation after anticoagulation. Further complications of endovascular interventions make these interventions a dilemma for most physicians. Therefore, exploration of optimized treatment strategies in CVST is necessary.

Hyperfibrinogenemia, decreased blood flow velocity, and increased viscosity of hyperfibrinogenemia are the three major factors that promote venous thrombosis (72). Batroxobin is a serine protease extracted from the venom of the snake Bothrops atrox moojeni, and it exerts defibrinogenating effects (13). Batroxobin reduces the concentration of fibrinogen in blood by degrading fibrinogen to fibrin degradation products (FDPs) and D-dimer (12, 13). The defibrinogenating effect of batroxobin improves microcirculation by reducing vascular resistance and increasing blood flow velocity (30). Batroxobin can also mobilize endothelial cells to release endogenous t-PA, which indirectly promotes thrombolysis (12, 13). Therefore, Batroxobin can play both preventative and therapeutic roles in patients with a high risk of CVST.

Despite the controversial effect of Batroxobin on coagulation status, the significant reduction of the amount of bleeding and the effect on hemostasis by Batroxobin was well studied. Batroxobin combined with anticoagulation can significantly promote the recanalization of CVST and cortical venous thrombosis (CCVT) without increasing the risk of bleeding (10, 11). Venous stasis and the embolism from the venous sinus, especially the superior sagittal sinus, were the main risks CCVT in CVT patients (73–75). CCVT is often secondary to venous infarct and hemorrhagic transformation. A previous study reported that Batroxobin reduced the death/apoptosis of damaged neurons, the size of the ischemic infarct, and the
risk of bleeding conversion (36). Therefore, CCVT patients are likely to benefit from Batroxobin treatment. CVST or venous infarct-induced cerebral edema resulted in a series of clinical symptoms of intracranial hypertension, which is often a predictor of poor prognosis (75, 76). Previous studies showed that CVST patients benefit from decompressive craniotomy (77). However, decompressive craniotomy might be better suited for severe cerebral edema caused by large venous infarcts. For CVST patients with mild intracranial hypertension caused by edema, Batroxobin may be a better choice since it reduces tissue edema and inhibits cytotoxic damage, as demonstrated in previous studies (14, 15, 42, 65).

CVST patients always showed good neurological and cognitive long-term outcomes (78). However, some patients also presented with significant neurological impairment or neuropsychological deficits due to the disruption of functional areas or conduction tracts when the cerebral cortex is infarcted because of CVST or thrombosis in the deep cerebral venous sinus (75, 79). Cognitive dysfunction is an important factor affecting patients’ quality of life and aggravating family burden. Therefore, in the acute stage of CVST or venous infarcts, intervention measures are needed to protect nerve cells in the damaged area to avoid or mitigate cognitive impairment as much as possible. Batroxobin improves free radical scavenging leading to neuroprotective function. A previous study reported that Batroxobin was effective in improving vascular cognitive impairment (VCI) caused by ischemic cerebrovascular disease after long-term treatment (24). Future studies are needed to investigate whether the cognitive dysfunction associated with CVST can benefit from the use of Batroxobin.

In summary, Batroxobin had broad clinical applications in both arterial and venous thrombosis, including promotion of thrombolysis, prevention of thrombotic formation, reduction of edema in infarcted areas, improvement of vascular cognitive dysfunction, and neuroprotection. The potential mechanisms include promotion of depolymerization of fibrinogen polymers, increase in the capacity of free radical scavenging, reduction of inflammation, and regulation of endogenous plasminogen activator expression. Batroxobin can also be therapeutic in CVST and their secondary diseases. However, the application of Batroxobin was still limited to clinical studies with small sample size. Future multi-centered studies with randomized design and larger sample size would provide more evidence on the potential effect of Batroxobin in cerebral vascular diseases.

CONCLUSION

Batroxobin could treat both arterial and venous ischemic diseases by promoting depolymerization of fibrinogen polymers, regulating the expression of related molecules, reducing oxidative stress, and reducing the inflammation response. However, current evidence of the beneficial effect of Batroxobin in cerebral vascular diseases was mostly from clinical and experimental studies with small sample size and high heterogeneity. Multi-centered clinical trials with randomized design and larger sample size would be needed in the future.

AUTHOR CONTRIBUTIONS

DL and SYS: manuscript drafting and revision, study concept and design, collection, assembly, and interpretation of the data. BLJ: collection, assembly, and interpretation of the data. RM, YHL, and SYS: manuscript drafting and revision, study concept and design, deeply edited the revised version and contributed critical revision, and final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.716778/full#supplementary-material

Supplementary Table 1 | PRISMA 2020 checklist.

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