Recirculatory Fibrinolytic-Assisted External Ventricular Drainage (EVD) for Intraventricular Hemorrhage

Zhen QIN (✉ zhen.qin@nmed.org.cn)

National Innovation Center for Advanced Medical Devices <https://orcid.org/0000-0002-6917-4418>

John Ching Kwong Kwok

Kwong Wah Hospital

Peter Yat Ming Woo

Kwong Wah Hospital

Carmen Yim

Kwong Wah Hospital

Chi Hang Chon

National Innovation Center for Advanced Medical Devices

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Abstract

Background

Elevated intracranial pressure and acute obstructive hydrocephalus secondary to intraventricular hemorrhage (IVH) can be treated by external ventricular drainage (EVD). The treatment time and the risk of EVD-related complications can be reduced with fibrinolytic agents' instillation via an EVD catheter, but previous clinical trial results did not reveal a significant improvement in terms of long-term functional outcomes. A recirculatory fibrinolytic-assisted EVD system was designed. The clot dissolution effectiveness of the system under different drug dosages and fluid flow rates was tested in an *ex vivo* model.

Results

The results showed that the mean clot mass was quickly reduced in an initial fibrinolytic agent dose-independent stage, followed by a dose-dependent stage. Elevating fibrinolytic agent dosages beyond a certain threshold did not contribute to shorter dissolution times. Optimal treatment parameters for such a system were determined. A recirculatory flow rate of 10–18 ml/min with a low-dose of 30 000–60 000 IU of uPA resulted in an 80% clot mass reduction within four hours.

Conclusions

This recirculating fibrinolytic system is a promising novel modification of conventional IVH treatment that could reduce clot dissolution times and procedure-related complications.

Background

Intracerebral hemorrhage (ICH) has an annual incidence of 10 to 30 per 100 000 people and accounts for 2 million, or 13%, of all newly diagnosed stroke cases worldwide [1–3]. The mortality rate is 30% and can result in significant disability [4, 2]. 40% of hemorrhagic stroke patients have concomitant intraventricular hemorrhage (IVH), which is an independent predictor for 30-day mortality and poor six-month functional outcomes [5–8, 4, 9–12]. The normalization of intracranial pressure (ICP) and the resumption of normal cerebrospinal fluid (CSF) circulation are dependent on efficient IVH clearance, which increases the likelihood of a good recovery.

External ventricular drainage (EVD) is a common procedure performed in daily neurosurgical practice for the treatment of IVH. Blood products and CSF are passively drained along a pressure gradient via an intraventricular catheter, and life-threatening obstructive hydrocephalus can be relieved [13–15, 7]. However, such catheters are at risk of occlusion, migration, and inducing central nervous system (CNS) infections such as bacterial meningitis or ventriculitis. Intraventricular fibrinolytic agent administration

via the catheter can reduce the risk of catheter occlusion and improve treatment outcomes. After instilling recombinant tissue plasminogen activator (rt-PA) [16–18] or urokinase plasminogen activator (uPA) [19–22, 12], the catheter is typically temporarily clamped for 60 minutes to allow time for clot dissolution. The catheter is subsequently reopened for the siphoning of blood products and CSF from the ventricular system. The process is generally repeated every 8 or 12 hours until IVH clearance is observed or when obstructive hydrocephalus is relieved on serial computed tomography (CT) scans. The treatment duration generally lasts 2 to 10 days. However, potential complications associated with intraventricular fibrinolytic drug instillation exist, including higher rates of neuro-inflammation, recurrent hemorrhage, and infection [23, 24, 7].

The causes for these procedure-related complications are believed to be associated with the mode of drug delivery and ineffectiveness of passive drainage. The fibrinolytic agent's movement into the clot is governed by its dosage concentration gradient at the clot surface. However, studies showed that increasing dosages failed to shorten the dissolution time beyond a threshold [25, 26]. Instead of increasing the dosage, which also increases the risk of neuro-inflammation or recurrent hemorrhage, the application of a flow/pressure gradient could assist drug penetration. Active drainage of the dissolved products could also contribute to faster clot removal. A closed-loop fluid circulation prototype system designed to drive fibrinolytic agent penetration into the clot was developed. The effects of the fluid flow gradient and the fibrinolytic agent concentration gradient on clot dissolution time were investigated in this study.

Methods

Clot Preparation

Clot volumes ranged from 10 ml – 50 ml [9, 5, 12, 4, 11]. In this study, 1.6 ml of 0.25 M calcium chloride was added to 20 ml of blood drawn from healthy donors (aged between 20 to 30 years) to reverse the intrinsic anticoagulation cascade [27]. The blood was then transferred into a warming receptacle at 37°C for 90 minutes.

Active EVD System Development

The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) is the most recent randomized placebo-controlled trial utilizing alteplase, a rt-PA, as the thrombolytic agent. However, rt-PA has been shown to elicit significantly more severe inflammatory processes when exposed to nervous tissue compared to uPA [28–31]. In addition, since uPA is more widely available in China and Southeast Asia, the agent was adopted for this study [21, 5, 20]. In clinical practice, uPA dosages prescribed for intraventricular instillation varies from 10 000 to 100 000 International Units (IU) constituted in 2 ml – 10 ml of saline solution. The drug is infused through the EVD catheter into the ventricular system every 8–12 hours [32, 33, 28, 20–22, 12]. As the entire treatment course generally lasts 2–10 days, the total uPA dosage can range from 40 000–3 000 000 IU. In this experiment, uPA (Urokinase – Green Cross Injection 60 000 IU, China Chemical & Pharmaceutical Co. Ltd; Taiwan Green Cross Co.

Ltd) of sequentially escalating doses of 6 000, 12 000, 30 000, and 60 000 IU was diluted in 50 ml of saline solution and transferred into the investigated active EVD system. Normal saline solution was used as the control infusion. An EVD catheter with an outer diameter (OD) of 3.1 mm and 20 inlet holes located within 27 mm from its tip (catalog number, 82-1735, Codman Neuro™, Depuy Synthes, Raynham [MA], USA) was used to deliver uPA. A co-axial microcatheter with an OD of 1.3 mm and inner diameter (ID) of 1.1 mm was used to drain CSF and lysed blood products. As the ID of most commercial EVD catheters range from 1.3 mm to 1.5 mm, the 1.1 mm ID of the microcatheter was not considered a potential risk factor for occlusion since continuous fluid pressure will be applied through the system. The drainage catheter and the uPA delivery catheter were connected to a container with 50 ml of uPA solution and a filter to separate blood products from CSF and uPA solution. Recirculatory flow was controlled by two peristaltic pumps.

Experiment Setup

The mass of the tested blood clots was first determined. They were then transferred into a polyethylene bag submerged in a 37°C water bath. The co-axial catheters were then inserted into the clot (Fig. 1). The flow settings were adjusted from 10–11 ml/min, 12–13 ml/min, 16–18 ml/min, to 20–24 ml/min, with drug delivery at a lower rate and fluid drainage at a higher rate.

The CLEAR III trial results concluded that poor functional outcome within the alteplase patient group was attributed to insufficient clot clearance. For every milliliter of clot remaining, the trial investigators observed a patient mortality hazard ratio of 1.03 and an mRS≤3 odds ratio of 0.96. A significant association was also identified between the attainment of > 80% of intraventricular clot clearance with both good functional outcome and lower mortality [34, 35]. In this study, clot mass was measured every 30 minutes on a precision balance until it fell below 20% of its initial mass and this was defined as the dissolution time. For the control tests, the experiment was halted after 8 hours of treatment. Each test was repeated three times.

Results

The mean initial clot mass was 21.7±0.9 g. The effects of flow rates on the percentage of clot mass change regarding uPA dosage are shown in Fig. 2 and Table 1. Clot mass reduction was rapid, independent of flow rates and uPA dosage in the first 30 minutes for all tests. Dependence on uPA dosage became apparent after 30 minutes, while the clot mass reduction in the control group saline tests were significantly slower. The remained clot after 2-hour treatment with 6 000 IU was 28.34%±10.85%, compared with 45.61%±7.16% for saline infusion (t-score = 9.04, p-value < 0.00001). In contrast, increasing flow rates only marginally increased the clot mass reduction in the control saline group tests. The remained clot after 2-hour treatment with 11 – 10 ml/min was 46.87%±3.05%, compared with 36.55% ±4.27% for 24 – 20 ml/min (t-score = 0.98, p-value = 0.43). The saline group results showed that infusion flow alone was responsible for approximately 60% of clot mass reduction.

Table 1. The dissolution time (hours) of clots under different uPA dosages and delivery-drainage rates

Dosage (IU)	10-11 ml/min	12-13 ml/min	16-18 ml/min	20-24 ml/min
6 000	7.39±1.55	4.89±0.53	2.50±0.5	4.59±0.63
12 000	6.67±0.31	3.54±0.44	2.53±0.94	3.54±0.19
30 000	3.50±0.39	3.22±0.37	2.56±0.54	2.80±0.36
60 000	3.62±0.66	3.28±1.11	2.07±0.82	3.22±0.29

A dose-response relationship between clot dissolution time and uPA dosage is shown in Fig. 3(a). Clot dissolution times were shortened with increased dosage for all flow conditions. For uPA dosages > 30 000 IU, the shortest clot dissolution times achieved were from 2–4 hours. Clot dissolution times were also shortened with increasing flow rates (Fig. 3(b)) with a minimum threshold rate of 16ml/min. These results suggest that 80% of clot mass reductions can be accomplished with a lower uPA dosages of 30 000 to 60 000 IU at an infusion flow rate > 16ml/min within 4 hours.

Discussion

Intraventricular hemorrhage is a commonly seen neurological emergency in 40% of patients with ICH and 50% of patients with subarachnoid hemorrhage (SAH) [36, 37]. Studies have shown that IVH is a poor independent prognostic factor for both types of hemorrhagic stroke [38]. The mortality rate of IVH complicating ICH is as high as 50%, with the volume of intraventricular blood being proportional to the risk of this outcome [37, 34]. Even among survivors of IVH, only 20% of patients were observed to have good functional outcomes [37].

The detrimental effects of IVH can be broadly classified into two causes: A) primary brain insult due to intracranial hypertension, either as a result of the hematoma volume per se or obstructive hydrocephalus; and B) secondary insult due to hematoma-induced cytotoxicity, oxidative stress, and neuroinflammation.

Both immediate and delayed hydrocephalus can occur as a consequence of IVH. The commonest immediate life-threatening cause is acute obstructive hydrocephalus from the blockage of normal CSF flow within the ventricular system. Studies also demonstrated that both the initial total hematoma volume and the duration of intraventricular hematoma presence before its dissolution were independent determinants of communicating hydrocephalus after the acute obstructive phase [39]. The CLEAR III trial showed that 44% of patients required permanent CSF shunting when ICP exceeded 30 mmHg [34]. In a population-based study, shunting was indicated in 18% of IVH patients, and shunt-dependence was identified as an independent predictor for long-term morbidity [40, 41].

Secondary brain injury due to IVH can occur due to disruption of the blood-CSF barrier, neuroinflammation, or cytotoxicity arising from blood components. Swine model studies have shown that obstructive hydrocephalus resulted in hypoperfusion changes of periventricular structures that persisted beyond hematoma resolution [42]. The ependymal surface, the thin single-layer epithelioid glial membrane that lines the ventricular system, are often damaged during IVH [42]. This results in dysregulation of the normal transfer of extracellular fluid, ions, and small molecules between the brain parenchyma and CSF [43, 44]. Iron, a degradation product of hemoglobin, is cytotoxic and can exacerbate oxidative injury [45, 46]. Normally, ependymal cells prevent excess iron deposition in the brain, but with their disruption following IVH, its accumulation can cause persistent hydrocephalus [47]. Inflammation, mediated by transforming growth factors (TGF- β 1 and TGF- β 2), has also been observed to cause obliterative arachnoiditis or dysfunction of the arachnoid granulations resulting in post-hemorrhagic communicating hydrocephalus [48, 49]. In animal studies, intraventricular injection of lysed red blood cells and iron led to a significant increase in ventricular volume and elevated CSF inflammatory markers [50]. These findings were supported by another study where aseptic CSF inflammation was detected in post-IVH brain tissue [44]. Intraventricular blood volumes were also positively correlated with more extensive neuroinflammatory responses reflected by elevated CSF white blood cell (WBC) counts [44].

Despite greater understanding of the multiple pathophysiological sequelae of IVH-induced secondary brain injury, current clinical management remains directed at ICP control. For patients with obstructive hydrocephalus, EVD functions both as therapeutic relief of intracranial hypertension and pressure monitoring. The efficacy of EVD for selected patients with IVH is widely accepted. The CLEAR III trial observed a proportional increase in mortality and poorer functional outcomes for every milliliter of clot remaining in the ventricular system, with 80% clot clearance being the determining threshold for improved outcomes [34]. However, drainage alone does not effectively assist clot dissolution. The mechanism of intraventricular blood clot lysis, similar to elsewhere in the body, is highly dependent on circulatory fibrinolytic activity. Unlike in the systemic vasculature, normal CSF does not contain fibrinolytic enzymes. Studies revealed that plasminogen and tissue plasminogen activator enzyme systems in IVH become saturated by 24–48 hours, and after that, further clot dissolution reaches a steady constant rate [51, 52]. This could explain why clot clearance with EVD alone is often frequently slow, lasting several days to weeks. In addition, ventricular catheter blockage by blood clots or by the choroid plexus often necessitates flushing or even repeated catheter revisions. The number of drainage system manipulations and duration of EVD are risk factors for bacterial ventriculitis and catheter-associated intraparenchymal tract hematomas [53].

The intraventricular administration of fibrinolytic agents through the ventricular catheter was introduced to facilitate clot dissolution and drainage in the 1990s [22]. Not only were catheter obstruction rates significantly reduced, but the duration required for clot clearance was also considerably shortened compared to EVD alone [38]. Meta-analyses showed that intraventricular fibrinolysis reduced IVH mortality by half and improved patient functional outcomes [54, 37, 55]. A recent systemic review also demonstrated a reduction in shunt dependence in patients that received such treatment [54].

Preclinical studies have observed that intraventricular rtPA could be neuro-toxic and pro-inflammatory [56–58]. A randomized-controlled trial noted that CSF cytokine concentrations, particularly tumor necrosis factor- α , interferon- γ , interleukin (IL)-1, IL-4, IL-6, and WBC counts were significantly elevated compared to placebo-treated patients [59]. There is also the theoretical risk of inducing further IVH with fibrinolytic agent instillation, although this has not been confirmed with RCTs [34]. Therefore, the duration and dosage of such drugs should be carefully titrated to balance clot lysis effects against its potential adverse effects.

Current intraventricular fibrinolytic agent administration involves temporarily clamping the catheter to permit CSF flow stasis after their introduction. As the blood clot is a crosslinked solid with micropores, drug permeation is primarily driven by a concentration gradient in a closed system. However, the rate and effectiveness of drug diffusion are difficult to monitor and studies demonstrated that merely increasing dosages did not shorten clot dissolution times [25, 26].

To increase clot dissolution, a prototype flow- and pressure- gradient actuated system with uPA was designed to accelerate drug permeation into the micropores of the clot. In this proof-of-concept study, we observed that this recirculatory fibrinolytic drug-assisted EVD system shortened clot clearance durations and required significantly lower overall uPA dosages. No catheter occlusions were observed during the treatment process. These findings may have clinical implications including reducing in-dwelling catheter durations along with its attendant related complications, decreasing the risk of neurotoxic blood degradation product exposure, and the minimizing the need for CSF shunting. The potential benefits of this novel system could translate to shortened hospitalization durations and improved functional outcomes.

Endoscopic-assisted microsurgical evacuation is an emerging technique for intraventricular clot removal. Clinical trials revealed higher clot removal rate, fewer complications, and better postoperative outcomes [60–62]. However, the operative time is significantly longer than EVD catheter placement. There is a steeper skill learning curve to attain procedure proficiency and often an experienced assistant is required to hold the neuro-endoscope. With such direct instrumental intraventricular clot manipulation close attention must be paid to avoid foramen, thalamic and thalamostriate vein injury that could result in catastrophic neurological consequences. Clots, especially during the acute phase, may be highly adherent to the ventricular wall unamenable to simple suction. The narrow working field of vision of a rigid neuro-endoscope's working channel also limits its capability to reach deep intraventricular locations, in particular the fourth ventricle. For these reasons, endoscopic-assisted microsurgical clot evacuations of IVH are not commonly performed and the efficacy and safety of this technique compared to EVD requires further investigation [63, 61, 64]. In view of these facts, it is believed that this novel recirculatory fibrinolytic drug assisted EVD system addresses the drawbacks of both these clot evacuation therapies.

There are several limitations to this study. First, the rate of clot dissolution is multifactorial. Apart from IVH volume, clearance is also affected by the clot's anatomical location and the relative position of the catheter. IVH within the third ventricle and the frontal horns of the lateral ventricles were subject to more

pronounced hematoma thrombolysis than elsewhere [65]. The morphology of the experimental receptacle containing the clot in our experiment was not a patient-driven anatomical replica of the ventricular system. Clinical studies showed that catheter placement on the side predominantly involved by IVH resulted in more rapid clot clearance [66]. Future studies investigating an active recirculatory drainage system of this nature should adopt a stereolithographic model of the ventricular system. Inter-individual variations in baseline serum plasminogen and platelet count levels influenced IVH resolution durations [52]. These factors were not controlled in the blood samples collected from healthy individuals in our study. Our model also did not consider ICP elevations that would require emergent relieving measures. Therefore, maintaining a closed EVD system without disruption of the thrombolytic fluid flow gradient is a design challenge that needs to be overcome before it can be clinically applicable. Finally, the possibility of rebleeding, natural history complications commonly encountered in clinical practice, could not be studied in our ex-vivo experimental model.

To conclude, this novel recirculatory fibrinolytic agent assisted EVD system demonstrated rapid hematoma clearance at significantly lower doses. A window of optimal flow and uPA dosage rates was determined in this study. Further, *in vivo* animal studies are required to address the model's limitations and to realize the potential clinical benefits for this novel IVH therapy.

Conclusions

EVD assisted by quasi-static fibrinolytic drug immersion can shorten blood clot mass reduction time. Replacing quasi-static drug immersion with drug recirculation significantly reduced treatment durations. A recirculatory fibrinolytic-assisted EVD system could clear 80% of the clot within four hours using a low uPA doses of less than 60 000IU. Patients with IVH may benefit from this novel clot clearance system.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. Ethics approval is not required as the blood samples were donated by the research team members voluntarily.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ZQ. The first draft of the manuscript was written by ZQ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

(a) Illustration of the experiment setup; (b) actual experiment setup

Figure 2

Average percentage change of clot weight treated with 4 different uPA dosages under: a) 11-10 ml/min; b) 13-12 ml/min; c) 18-16 ml/min; d) 24-20 ml/min.

Figure 3

Dose-response relationship of clot dissolution against a) uPA dosage; b) drug delivery rate.