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EDITORIAL

An Update On Medical Treatment for Intracerebral Hemorrhage

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Intracerebral hemorrhage (ICH), as a kind of hemorrhage stroke, is characterized by high morbidity, mortality, and disability rates, which is a most serious disease in neurosurgery [1, 2]. There are about 2 million new cases of ICH around the world every year, and the incidence is as high as 20~30% in Asia, which is a serious threat to human health [3]. ICH is caused by the rupture of blood vessels, and blood flows into the surrounding brain parenchyma. As the global population ages, the incidence of ICH is predicted to increase. Therefore, understanding the pathogenesis of ICH and identification of novel targets are helpful to researchers for developing new drugs for ICH therapy. The aim of this editorial is to summarize the development of preclinical and clinical medical treatments for ICH.

At the onset of ICH, within the first few hours, the bleeding leads to the formation of hematoma and mechanical damage to adjacent tissues, which results in a sharp increase in intracranial pressure and induces primary brain injury [4]. At present, surgical operation is adopted to remove hematoma and reduce the intracranial pressure [5]. The Surgical Trail in Intracerebral Hemorrhage (STICH) has failed to provide positive evidence to support the effect of surgical operation, and STICH2 also showed no benefit (NCT01320423) [6, 7]. However, surgical removal the hematoma after ICH shows only rarely effects in neurological recovery, and the outcomes for the patients are unsatisfied. Furthermore, some clinical trials on blood pressure medications showed no benefit, including intensive blood pressure reduction in acute cerebral hemorrhage trial 2 (INTERACT2, NCT00716079), ICH-ADAPT (NCT00963976), and ATACH-2 (NCT00226096) [8–10]. In addition, hematoma expansion also could be a target for ICH therapy. There are some clinical trials are tested targeting on haematoma expansion, like recombinant activated factor VIIα (SPOTLIGHT, NCT01359202; STOP-IT, NCT00810888) [11]. Recently, Vitamin K1 in the treatment of spontaneous ICH is tested in the phase I (NCT03388970, https://clinicaltrials.gov/ct2/show/ NCT03388970). And tranexamic acid is being tested for ICH by inhibiting haematoma expansion at phage 3 superiority trial (TICH2, ISRCTN93732214) [12]. Whereas, these clinical trials targeting on primary brain injury may reduce the hematoma growth, but cannot improve the functional outcomes of the patients. About 40% of the surviving patients bear obvious disabilities with the treatment of surgery, which seriously affecting the life quality of the patients. Secondary brain injury (SBI) is an important factor affecting the outcomes of ICH patients. Therefore, ICH-induced SBI has been focused on for researching novel therapeutic targets for ICH.

The pathophysiological mechanisms of the hematomas surroundings are complex after ICH. Except for toxic injury of hematoma itself, there are a variety of damage factors involved in, including oxidative stress, neuronal programmed cell death (apoptosis, necrosis, etc.), mitochondrial injury, inflammatory response, excitatory neurotransmitter transmission, and blood-brain-barrier (BBB) damage. These are all the therapeutic targets for ICH, and much work has been done in the preclinical research. Compared with the preclinical researches, there are only a few clinical trials targeting on SBI after ICH. Here, we summarize some preclinical and clinical treatment strategies or trials for ICH-induced SBI therapy.

First of all, the major contributors of brain injury released from haematoma are considered to hemoglobin and iron [13, 14]. Deferoxamine (DFX), an iron chelator, has been reported to reduce neuronal death, hematoma lysis, microglia activation, and other damage after ICH [15–20]. Also, DFX has been tested in several clinical trials (NCT02175225, NCT02367248, NCT00526214) for ICH therapy, even though there are no results available [21, 22]. Inhibition or deletion the hem oxygenase, an enzyme which release irons

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from haem, could also reduce SBI induced by ICH [23]. Thrombin, another important hematoma component, can also initiate neuronal or astrocytes apoptosis and induce microglia activation, which might contribute to excitoxicity, inflammation and BBB leakage [24–26]. Inhibition of thrombin has been reported to show reduction of brain injury induced by ICH [27]. In the other hand, a low concentration of thrombin could prevent rebleeding and protect neurons and astrocytes from cell death [2, 28]. During ICH, the hematoma component release may cause brain damage by generating free radicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals' accumulation in brain tissues could damage neurons and endothelial cells, and induce microglia activation. Therefore, the scavengers of free radicals, such as melatonin, edaravone, isoliquiritigenin, acetazolamide, and so on, show improvement effects on ICH-induced SBI by inhibiting oxidative stress in the preclinical researches [29–33]. However, the clinical trial is not satisfactory. NXY-059 (disufenton sodium), a nitrone free radical scavenger, show no benefit with the placebo group (NCT00075959) [34]. The reasons for these negative results relate to the NXY-059 may be inability to scavenge the high amounts of free radicals induced by ICH [34].

ICH could induce perihematomal cell death, including apoptosis, necroptosis, autophagy, and ferroptosis [20]. Therefore, protecting neurons from cell death may reduce brain injury after ICH. Lots of compounds, factors, or drugs have been reported in the animal models to reduce SBI during ICH by inhibiting neuronal apoptosis [35, 36]. For example, warfarin pretreatment exhibits benefit to experimental ICH by reducing cell death [37]; recombinant osteopontin (rOPN) improves neurological function recovery by protecting against apoptosis following ICH [38]. In the clinical trial, an apoptotic inhibitor, tauoursodeoxycholic acid (TUDCA), is being test for ICH [39]. Recently, necroptosis and ferroptosis have been reported to play an essential role in ICH-induced SBI, which could be targets for improving ICH [40–43]. Autophagy, another programmed cell death way, also participate in ICH-induced SBI, even though whether the role of this cell death pathway is beneficial or harmful is unclear [44, 45]. Moreover, glutamate-induced excitoxicity, as the main excitatory neurotransmitter in the central nervous system (CNS), plays a critical role in neuronal cell death after ICH. Glutamate-induced excitoxicity is mediated by N-methyl-D-aspartate (NMDA) receptors, and it has been reported that NMDA receptor inhibition could reduce glucose hypermetabolism and improve brain injury after ICH [46, 47]. The NMDR antagonist, CP-101,606 (traxoprodil), has been tested in clinical trial for stroke (NCT00073476), which has been terminated. Also, the effect of CP-101,606 has been focused on traumatic brain injury [48]. In addition, targeting on NMDA receptor has been studied for ICH therapy in some animal models. IL-6 antagonist, LMT-28, blocks the accumulation of damage after ICH by inhibiting activation of NMDA receptor [49].

In ICH, inflammation begins from the release of irons after formation of hematoma. Thus, inflammation could be one of major causes of poor outcomes of ICH, with microglia activation, an influx of leucocytes (neutrophils, monocyte and lymphocytes) into the brain, and leading to production of proinflammatory cytokines (tumor necrosis factor α, interleukin 1 β, etc.), chemokines, adhesion molecular, matrix metalloproteinase (MMP, MMP9 and MMP3), and cell death products, which could disrupt BBB and destroy surrounding tissues [2, 26, 50–57]. Therefore, brain inflammation has become a critical modifiable determinant target for the development of ICH-induced SBI treatment [5, 58]. Due to the mitigation of inflammation, celecoxib, a cyclooxygenase-2 inhibitor, has been investigated in the ICH pilot clinical trial (NCT00526214) [59]. Pioglitazone, another drug which show anti-inflammation effect in ICH therapy, is being studied in a phase 2 clinical trial (SHRINC, NCT00827892, https://www.clinicaltrials.gov/ct2/show/ NCT00827892?term=NCT00827892&rank=1). Experimental research suggests that statins, competitive inhibitors of hydroxy-3-methylglutary1 coenzyme A (HMG-CoA reductase), may reduce inflammation and free radicals after brain injury [60–62]. A clinical trial of rosuvastatin for ICH (NCT00364559) showed a positive results, whereas a trial for simvastatin was terminated (NCT00718328) owing to its poor enrolment [62]. As a core factor in neuroinflammation, microglia activation is targeted for ICH therapy [63–65]. Microglia constantly survey the inflammatory process through the pattern recognition receptors (PRRs), including toll like receptors (TLRs) and nucleotide-binding oligomerization domain like receptors (NLRs). TLR2 and TLR4, as important PRRs, could be activated by the components of hematomas and induce neuroinflammation after ICH, showing that TLR antagonists could be used to attenuate brain injury [66, 67]. The inhibitors of TLR2 or TLR4, including curcumin, isoliquiritigenin, melatonin, TAK-242, M62812, and so on, have been investigated to inhibiting inflammation after brain injury, whereas their benefit effects for ICH will be further evaluated in the clinic [68–73]. In addition, nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), one of NLR family members, could be involved in some inflammation-related disease and plays a critical role in host defense against infection [64]. NLRP3 inflammasome activation has been suggested as a target for ICH-induced neuroinflammatory control, and NLRP3 inhibitor (MCC950) would be a potential candidate for ICH therapy [50, 74]. Furthermore, some intracellular molecules could stimulate inflammation effect directly after ICH. High-mobility group protein box-1 (HMGB1), which is released from necrotic cells or secreted by microglia, has been reported to participate in ICH-induced inflammation injury.

Inhibitor of HMGB1 by preventing its release or inhibiting its activity directly would be benefit to attenuate neuroinflammation. The inhibitor of HMGB1, glycyrrhizin, binds to HMGB-1 to inhibit its activity, which could reduce brain edema after ICH [75]. On another hand, ethyl pyruvate (EP) exert neuroprotective effect via inhibiting HMGB-1/TLR4 inflammation signaling pathway and reducing neuronal apoptosis to decrease HMGB1 release [76, 77].

As a result of inflammation, breakdown of the BBB takes place during SBI after ICH. As well, this progress could contribute to inflammation by promoting leucocyte infiltration. Injury to BBB is a key feature of ICH and may contribute to perihematomal cell injury. Thus, finding methods to protect BBB from leakage represents a promising approach to ICH-induced SBI therapy. There are several events that may cause BBB disruption, including endothelial cell death or transcytosis increasing, and alteration in the junctions [78, 79]. Several approaches have been reported to show improvement effect in brain injury via reducing BBB disruption and junction changes after ICH. Curcumin, tempol, carnosine, cerebrolysin, baicalin, Hydrogen sulfide and some other compounds, inhibitors, or siRNA have been studied in the preclinic for ICH therapy, which could attenuate BBB leakage through regulating tight junction (TJ) proteins (ZO-1, occluding, claudin-5, etc.) or inhibiting inflammation [80–87]. Preventing the translocation of TJ proteins from plasma membrane could also improve the BBB disruption after ICH, which may be achieved by inhibiting endocytosis trafficking, showing that Msfd2a could be a potential target [88]. Inhibiting cytoskeletal reorganization and stressing the formation of fiber may be another strategy [89]. Overexpression of heat shock protein 27 (HSP27) ameliorates BBB disruption after brain injury [90]. In addition, loss of annexin A1 in the cerebrovascular endothelium has been reported, and administration of recombinant annexin A1 could prevent ICH-induced BBB dysfunction [91]. Moreover, MMPs play critical roles in loss of TJ proteins and BBB leakage after ICH. Inhibitors of MMPs could reduce ICH-induced brain edema and BBB disruption [92, 93]. A MMP9 selective inhibitor, SB-3CT, could also protect the BBB disfunction after brain injury [94]. However, there is no clinical trials targeting on BBB disruption for ICH therapy, and the reasons maybe relate to the complex pathways involved in the TJ protein changes.

In summary, ICH is the highest mortality stroke subtype in the clinic. More and more evidences have shown that many cellular and molecular mechanisms are participated in ICH-induced brain injury [2]. And, increasing therapeutic targets have been explored for novel drugs in the ICH preclinical research [95]. Blood pressure management drugs, recombinant activated factor VIIα, and tissue plasminogen activator have been used for improving primary brain injury by reducing blood pressure and inhibiting hematoma expansion after ICH [11, 96, 97]. Furthermore, many compounds, recombinant proteins, drugs and other agents including glibenclamide, suberoylanilide hydroxamic acid, adropin, recombinant C1q/TNF-related protein 9 (rCTRR9), melatonin and so on, have been reported to exhibit neuroprotective effects during ICH via reducing neuronal cell apoptosis, inhibiting inflammation or protecting BBB [29, 98–101]. Genetic modifications are also used and researched in ICH treatment. However, serious side effects would be caused, and the safety has not been considered. So far, there is no neuroprotective agent as ever been shown to be beneficial in clinical trial. Therefore, it is necessary to our researchers for seeking of novel safe and effective strategies and agents, which is hoped to have positive findings in the clinical trials.

Compliance with Ethical Standards

The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. And there is no human or animal subject in this article.

Conflict of Interest The authors declare that they have no conflict of interest.

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