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Vagus nerve stimulation in intracerebral hemorrhage: the need for further research

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Vagus nerve stimulation (VNS) and stroke: Stroke is the second leading cause of death and the third leading cause of disability worldwide (Baig et al., 2023). There have been significant paradigm shifts in the management of acute ischemic stroke through mechanical thrombectomy. In chronic ischemic stroke, invasive VNS paired with rehabilitation is associated with a significant increase in upper limb motor recovery and is FDA-approved (Baig et al., 2023). There are no treatments of similar efficacy in acute intracerebral hemorrhage (ICH) where several promising trials, e.g., TICH-2, STOP-AUST, and TRAIGE did not show improvements in functional outcomes (Puy et al., 2023).

Ongoing trials are investigating the efficacy of non-invasive, transcutaneous vagus nerve stimulation (tVNS) for neuroprotection in acute ischemic stroke [NCT04050501], acute subarachnoid hemorrhage [NCT04557618] and as a tool to promote recovery in chronic ischemic stroke [ISRCTN20221867]. Although some clinical trials have evaluated VNS in stroke cohorts that include ICH, no clinical trials have been specifically designed for ICH. The exclusion of ICH represents a missed opportunity to develop an inclusive evidence base for post-stroke recovery. It may also exacerbate global inequity given the greater relative burden of hemorrhagic stroke in low and middle-income countries (Puy et al., 2023).

In this perspective, we outline the rationale for greater inclusion of people with ICH in trials of vagus nerve stimulation.

Pre-clinical evidence for VNS in ICH: ***Acute stroke:*** Whilst the acute vascular insult in ischemic and hemorrhagic stroke may differ, they share multiple risk factors, aetiologic pathophysiology of endothelial dysfunction and secondary inflammatory cascades that drive neurological injury (Puy et al., 2023). For instance, ischemic and hemorrhagic stroke may both arise in the context of advancing age, hypertension, and endothelial dysfunction. In the acute phase, disruption of blood supply results in oligaemia, excitotoxicity, generation of reactive oxygen species, mitochondrial dysfunction, disruption of the blood–brain barrier, and cerebral edema (Puy et al., 2023).

There are several potential mechanisms through which VNS is postulated to impact acute ischemic stroke that are pertinent to ICH. These include increasing cerebral blood flow, reducing excitotoxicity, post-stroke inflammatory cascades, and apoptosis, and stabilization of the blood–brain barrier (Baig et al., 2023). These effects may mitigate the mechanisms of stroke-related injury and provide a strong rationale for the potential utility of VNS in acute ICH. For instance, VNS-mediated reductions in pro-inflammatory cell recruitment and activity of matrix metalloproteinases could feasibly reduce blood–brain barrier breakdown (Baig et al., 2023). This could result in reduced edema that damages the peri-hematomal tissue and may also mitigate against rises in intracranial pressure due to CSF obstruction. **Figure 1** illustrates some of the post-ICH pathophysiology and demonstrates where VNS may offer plausible benefits.

Similarly, traumatic brain injury shares a common pathophysiology with primary ICH where, following a mechanical brain injury, a range of secondary injuries including excitotoxicity, neuroinflammation, oxidative stress, and apoptosis arise (Srihagulang et al., 2022). VNS has been shown to mitigate these secondary effects in animal models of traumatic brain injury (Srihagulang et al., 2022). This strengthens the case for further research of VNS in ICH.

Chronic stroke: In chronic stroke, both ischemia and ICH lead to liquefactive necrosis of the affected brain region. The adaptive changes that occur with recovery after a stroke depend on the degree and location of the injury. They include various types of functional reorganization such as reversal of diaschisis (the sudden change in function of structurally distant brain regions that are functionally connected to the damaged region), angiogenesis, axonal sprouting, and synaptic remodeling in the perilesional regions and the debatable adaptive role of the contralesional hemisphere (Pekna et al., 2012).

In rodent models of ischemic stroke, invasive VNS paired with rehabilitation has been demonstrated to be more effective than rehabilitation alone (Andalib et al., 2023). This has been shown to be associated with increased synaptic connectivity in corticospinal tract motor networks specific to the rehabilitated forelimb (Andalib et al., 2023). Evidence from tVNS in the subacute phase after ischemic stroke also signifies the role of increased expression of BDNF, and angiogenesis in VNS-mediated functional recovery (Baig et al., 2023). Response to rehabilitation alone after ICH shares some underlying mechanisms to ischemic stroke including synaptogenesis in the ipsilateral motor cortex (Auriat and Colbourne, 2009). It follows that VNS may potentiate rehabilitation-mediated adaptations in ICH.

Invasive VNS paired with rehabilitation has been shown to increase forelimb recovery in a rodent model of ICH that included damage to both white and grey matter (Hays et al., 2014). In this study, VNS paired with rehabilitation started at ≥ 9 days post-ICH; the improvement in neurological function was not associated with lesion size suggesting that the mechanism of recovery was through neuroplasticity rather than neuroprotection. Whilst there are fewer studies exploring the mechanism of VNS in recovery after ICH, the known mechanisms in ischemic stroke support further inquiry in translational research of ICH.

Clinical evidence for VNS in ICH: Trials of therapies to enhance neuroplasticity are essential to help mitigate the burden of stroke. In studies of invasive VNS, such as the vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischemic stroke (VNS-REHAB) study, none of the included participants had ICH. In eight clinical trials of tVNS in acute or chronic stroke, six have included participants with ICH. However, from the available data, of the 185 participants across these studies, only 43 (23%) had ICH (Capone et al., 2017; Chang et al., 2021; Arsava et al., 2022; Badran et al., 2023; Baig et al., 2023; Wang et al., 2024). Whilst this is an underpowered sample to draw definitive conclusions about the efficacy of VNS in this population, there are important observations that can be made.

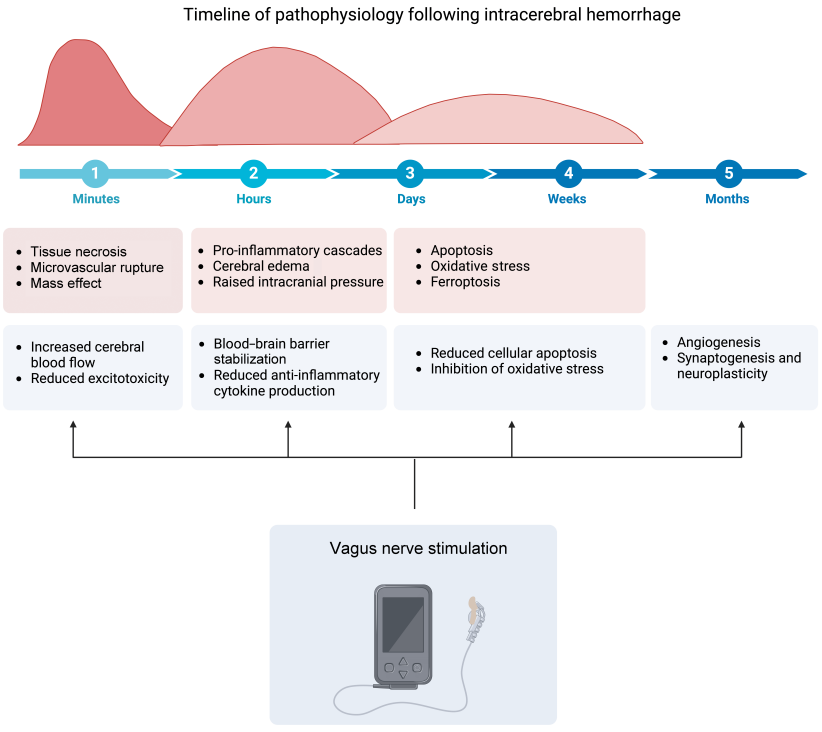

Figure 1 | **Mechanisms of vagus nerve stimulation relevant to the pathophysiology of intracerebral hemorrhage.**
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Acute stroke: In acute stroke, invasive VNS is not feasible but non-invasive alternatives may be of clinical utility. The TR-VENUS study demonstrated the safety and feasibility of cervical tVNS in acute ischemic stroke (61 participants) and ICH (8 participants) (Arsava et al., 2022). Participants received either sham, low-dose, or high-dose tVNS. Of the eight participants with ICH, one received sham tVNS and seven received high dose tVNS. Whilst no conclusions can be drawn about the efficacy of tVNS from this small, asymmetrical cohort, no participants experienced > 30% increased hematoma growth or clinical deterioration by 24 hours post-ICH.

Subacute and chronic stroke: Capone et al. (2017) published the first study of tVNS to include ischemic stroke and ICH. Twelve participants completed a 10-day intervention of tVNS or sham tVNS prior to robotic rehabilitation therapy. Four (two active and two sham) of these participants had an ICH as their index event. Both individuals with ICH who had active tVNS had a 3-point increase in upper limb Fugl-Meyer total motor score (ULFM) after 10 days compared to the two individuals with sham tVNS who had a 0 and 1-point increase, respectively. There were no safety concerns in the ICH cohort. A later study of tVNS with robotic rehabilitation included 36 individuals with chronic supratentorial stroke included 9 (25%) with ICH (Chang et al., 2021). Here, 9 × 1 hour sessions were delivered over 3 weeks. There were significant improvements in hand and wrist spasticity in the active group although individual differences in participants with ICH were not reported. Li et al. (2022) demonstrated that 4 weeks of tVNS prior to rehabilitation in subacute stroke could lead to sustained improvements in sensorimotor function at 12 months; however, only 5 of the 60 participants included had ICH. This is consistent with results from Wang et al. (2024), where tVNS paired with rehabilitation over 4 weeks was associated with a 7-point increase in ULFM compared to sham; 32.5% of the participants in this study had supratentorial ICH. From these studies, relatively short periods of tVNS may be associated with improvements in flexor synergy and spasticity in people with ICH. However, the total number of participants with ICH included in studies remains low.

No randomized controlled trials of invasive VNS have included participants with ICH. However, in a recent case report, a patient with a 3-year history of putaminal ICH underwent VNS implantation and experienced a 14-point increase in ULFM after 6 weeks (minimum clinically important difference of 6) (Cummins et al., 2024). This illustrative case provides hope for the potential efficacy of VNS in ICH.

Challenges: There are difficulties in extrapolating the studies of VNS in ischemic stroke into ICH. First, there are unique aspects to the pathophysiology of ICH-mediated injury including, but not limited to, thrombin formation, iron-induced injury, vasogenic edema, and rises in intracranial pressure (Puy et al., 2023). This may be most relevant in the acute stages whereas, in the chronic phase, the consequences of both stroke subtypes are similar. In some studies, VNS has been demonstrated to increase cerebral blood flow in the acute stages of ischemic stroke (Andalib et al., 2023); it is not known whether the overall effect of this would be to improve perfusion of the salvageable peri-hematomal tissue or whether it may potentially exacerbate hematoma expansion. Second, a large proportion of ICH is related to hypertension and affects the subcortical white matter. It is not clear whether VNS-mediated improvements preferentially affect the cortex or corticospinal tracts in clinical populations. Evidence from a subgroup analysis of the pivotal VNS-REHAB trial suggests that the presence or absence of cortical involvement did not influence ULFM response following VNS and rehabilitation (Dawson et al., 2023). Third, as ICH is less common than ischemic stroke, clinical trials where both ischemic stroke and ICH are included would require inflated sample sizes to allow comparison in subgroup analysis. Further effective treatments for acute ICH may need rapid, early administration e.g., in unstratified pre-hospital cohorts where sample sizes will need to account for the presence of stroke mimics. Fourth, severe ICH can be complicated by intraventricular extension, hydrocephalus, and the need for neurosurgery, all of which may delay intervention with VNS or potentially affect the ceiling of improvement.

Future directions: VNS is highly promising as a potential treatment option in both ischemic stroke and ICH. Whilst there is a shared pathophysiology between both conditions, further pre-clinical data are required in animal models of ICH to determine the mechanisms of neuroprotection and neuroplasticity in different brain regions. It remains to be determined whether the principal effects of VNS in ICH are mediated through changes in cortical neuroplasticity or white matter connectivity. Adequately powered clinical trials either including people with ICH or specifically designed for ICH are necessary to establish whether VNS is impactful in this population in both the acute and chronic settings.

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